PCT/IB 04 / 00208

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PATENT COOPERATION TREATY (PCT)
TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS (PCT)

CERTIFIED COPY OF THE INTERNATIONAL APPLICATION AS FILED AND OF ANY CORRECTIONS THERETO

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International Application No. / Demande internationale n° PCT/IB 0 3 / 0 4 7 4 1

International Filing Date / Date du dépôt international 28 OCTOBER 2003 (28. 10. 03)

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International Bureau of the World Intellectual Property Organization (WIPO)

Bureau International de l'Organisation Mondiale de la Propriété Intellectuelle (OMPI)

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Head, PCT Receiving Office Section
Chef de la section "office récepteur du PCT"

792MAS02

PCT REQUEST

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0	For receiving Office use only	
0-1	International Application No.	PCT/IB 03/04741
0-2	International Filing Date	28 OCTOBER 2003
0-3	Name of receiving Office and "PCT International Application"	INTERNATIONAL BUREAU OF WIPO PCT International Application
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.07.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	International Bureau of the World Intellectual Property Organization (RO/IB)
0-7	Applicant's or agent's file reference	792MAS02
I	Title of invention	NOVEL COMPOUNDS AND THEIR USE IN MEDICINE: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM
II	Applicant	
II-1	This person is:	applicant only
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III-5	Applicant and/or inventor	
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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	28 October 2002 (28.10.2002)
VI-1-2	Number	792/MAS/02
VI-1-3	Country	IN
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

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VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	GURRAM, Ranga, Madhavan
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VIII-4-1-1-3	Mailing address:	Dr. Reddy's Laboratories Limited Bollaram Road, Miyapur
VIII-4-1-1-4	Citizenship:	IN
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

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VIII-4-1 -2-1	Name:	BHUNIYA, Debnath
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VIII-4-1 -2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1 -3-1	Name:	DAS, Saibal, Kumar
VIII-4-1 -3-2	Residence: (city and either US State, if applicable, or country)	Hyderabad, Andhra Pradesh, India
VIII-4-1 -3-3	Mailing address:	Dr. Reddy's Laboratories Limited Bollaram Road, Miyapur
VIII-4-1 -3-4	Citizenship:	IN
VIII-4-1 -3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

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VIII-4-1-4-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
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VIII-4-1-5-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
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VIII-4-1-6-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-6-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

PCT / IB 03 / 04741

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	11 10 A	-
IX-2	Description	57	-
IX-3	Claims	18	-
IX-4	Abstract	1 1 0 A	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	87 85 A	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	DR. REDDY'S LABORATORIES LIMITED	
X-1-2	Name of signatory	Dr. V. M. Sharma	
X-1-3	Capacity	Associate Research Director	

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10-1	Date of actual receipt of the purported international application	27 OCTOBER 2003 27.10.03
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	28 OCTOBER 2003 28.10.03
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

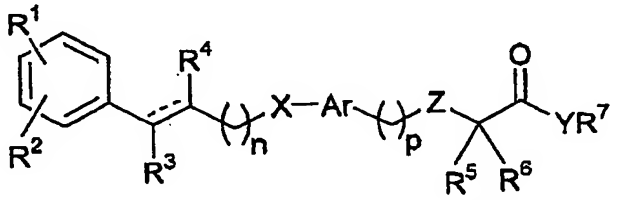
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

NOVEL COMPOUNDS AND THEIR USE IN MEDICINE: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Field of the Invention

The present invention relates to novel hypolipidemic, antiobesity, hypocholesterolemic and antidiabetic compounds. More particularly, the present invention relates to novel alkyl carboxylic acids of the general formula (I), pharmaceutically acceptable salts thereof as well as pharmaceutical compositions containing them.



(I)

where R^1 and R^2 may be same or different and independently represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted group selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroarylcarbonyl, aryloxy, aralkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, heteroarylcarbonylamino, heteroaryl, heterocyclyl, heteroaralkoxy, heteroaryloxy, fluorenylmethoxycarbonyl (Fmoc), fluorenylmethoxycarbonylamino (N-Fmoc), -OSO_2R^8, -$OCONR^8R^9$, NR^8COOR^9, -NR^8COR^9, -NR^8R^9, -$NR^8SO_2R^9$, $NR^8CONR^9R^{10}$, -$NR^8CSNR^8R^9$, -SO_2R^8, -SOR^8, -SR^8, -$SO_2NR^8R^9$, -SO_2OR^8, $CONR^8R^9$, $COOR^9$, COR^9, wherein R^8, R^9 and R^{10} may be same or different and independently represent hydrogen, alkyl, aryl, aralkyl, aryloxy or heteroaryl or R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring, which may optionally contain up to 3 heteroatoms selected from N, S, or O and may be unsubstituted or have up to 4 substituents which may be identical or different.

R^3 and R^4 may be same or different and independently represent hydrogen, halogen, optionally substituted alkyl, cycloalkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group.

'n' and 'p' represent 0-6.

X represents O, S, NR where R represents hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, alkanoyl, or aroyl.

Ar represents optionally substituted, divalent, single or fused aromatic, heteroaromatic or heterocyclic group.

Z represents O, S, NR where R is as defined above.

R^5 and R^6 may be same or different and independently represent hydrogen, hydroxy, halogen or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, aryl, aralkyl or heteroaralkyl groups. R^5 and R^6 together may form a 5 or 6 membered cyclic rings, which may contain one or two hetero atoms selected from O, S or N.

Y represents oxygen or NR^{11} where R^{11} represent hydrogen, optionally substituted groups selected from alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl or heteroaryl.

R^7 and R^{11} together may also form a 5 or 6 membered cyclic ring, which may contain one or two hetero atoms selected from O, S or N.

'—-' represents a bond or no bond.

The present invention also relates to a process for the preparation of the above said compounds.

The compounds of the present invention lower plasma glucose, triglycerides, lower total cholesterol (TC) and increase high density lipoprotein (HDL) and decrease low density lipoprotein (LDL), which have a beneficial effect on coronary heart disease and atherosclerosis.

The compounds of general formula (I) are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of hyperlipidemia, hyperglycemia, hypercholesterolemia, lowering of atherogenic lipoproteins, VLDL (very low density lipoprotein) and LDL. The compounds of the present invention can be used for the treatment of renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The compounds of general formula (I) are also useful for the treatment and/or prophylaxis of leptin resistance, impaired glucose tolerance, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, eating disorders, inflammation and for the treatment of cancer. The compounds of the present invention are also useful in the treatment and/or prophylaxis of the above said diseases in combination/concomittant with one or more HMG CoA reductase inhibitor; cholesterol absorption inhibitor; antiobesity

drug; lipoprotein disorder treatment drug; hypoglycemic agent: insulin; biguanide; sulfonylurea; thiazolidinedione; dual PPARα and γ or a mixture thereof.

Background of the Invention

Atherosclerosis and other peripheral vascular diseases affect the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and development of effective therapeutic strategies.

Statins and fibrates are the more widely used drugs for the treatment of the hyperlipidemia. Statins act *via* HMG CoA reductase enzyme there by cholesterol biosynthesis. The predominant effect of statins is lowering the levels of LDL cholesterols (LDL-C). Fibrates another class of hyperlipidemic compounds are known to be weak agonist of Peroxisome Proliferator Activated Receptor (PPAR)-α subtypes. Peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor super family. The gamma (γ) isoform of PPAR (PPARγ) has been implicated in regulating differentiation of adipocytes (*Endocrinology*, 135 (1994) 798-800) and energy homeostasis (*Cell*, 83 (1995) 803-812), whereas the alpha (α) isoform of PPAR (PPARα) mediates fatty acid oxidation (*Trend. Endocrin. Metab.*, 4 (1993) 291-296) thereby resulting in reduction of circulating free fatty acid in plasma (*Current Biol.* 5 (1995) 618-621). PPARα agonists have been found useful for the treatment of obesity (WO 97/36579). A wealth of information exists on the influence of fibrates as PPAR-α agonists on the cardiovascular risk profile. These compounds correct atherogenic dyslipoproteinemia. Several angiographic intervention trials show a decreases incidence of cardiovascular events *(Trends in Pharmaceutical Sciences 2001, 22(9), 441-443)*. It has been recently disclosed that compounds, which are agonists for both PPARα and PPARγ are suggested to be useful for the treatment of syndrome X (WO 97/25042). Similar effect between the insulin sensitizer (PPARγ agonist) and HMG CoA reductase inhibitor has been observed which may be useful for the treatment of atherosclerosis and xanthoma (EP 0 753 298).

It is known that PPARγ plays an important role in adipocyte differentiation (*Cell*, 87 (1996) 377-389). Ligand activation of PPAR is sufficient to cause complete terminal differentiation (*Cell*, 79 (1994) 1147-1156) including cell cycle withdrawal. PPARγ is consistently expressed in certain cells and activation of this nuclear receptor with PPARγ agonists would stimulate the terminal differentiation of adipocyte precursors and cause

morphological and molecular changes characteristics of a more differentiated, less malignant state (*Molecular Cell*, (1998), 465-470; *Carcinogenesis*, (1998), 1949-53; *Proc. Natl. Acad. Sci.*, 94 (1997) 237-241) and inhibition of expression of prostate cancer tissue (*Cancer Research* 58 (1998) 3344-3352). This would be useful in the treatment of certain types of cancer, which express PPARγ and could lead to a quite nontoxic chemotherapy.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in the general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), Intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlationship between CAD and atherosclerosis with serum HDL-cholesterol concentrations (Stampfer *et al., N. Engl. J. Med.*, 325 (1991), 373-381). The risk of CAD increases with increasing levels of LDL and VLDL.

Atherosclerosis coronary artery disease is fast becoming a major cause for mortality both the developing and developed nations. It has been demonstrated that abnormal cholesterol levels play a major role for morbidity and mortality, and aggressive treatment saves lives. Clinical trials have demonstrated convincing benefits of cholesterol lowering, for reducing myo cardial infarction among patients with CHD as well as for decreasing the incidents of cardiac events in patients without established coronary disease (*JAMA 2001, 285 (19), 2508-2509).*

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.*, (*Br. Med. J.*, 282 (1981), 1741-1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of human, and high level of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al., Arteriosclerosis* 6 (1986) 434-441 have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer it to liver, which is known as reverse cholesterol transport, (Macikinnon *et al., J. Biol. chem.* 261 (1986), 2548-2552). Therefore, agents that increase HDL cholesterol

would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems.

Diabetes and/or insulin resistance is yet another disease which severely effects the quality of large population in the world. Insulin resistance is the diminished ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably raises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of abnormalities including obesity, hypertension, hyperlipidemia (*J. Clin. Invest.*, 75 (1985) 809-817; *N. Engl. J. Med* 317 (1987) 350-357; *J. Clin. Endocrinol. Metab.*, 66 (1988) 580-583; *J. Clin. Invest.*, 68 (1975) 957 - 969) and other renal complications (patent publication No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

Hyperlipidemia is the primary cause for cardiovascular (CVD) and other peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance/insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases.

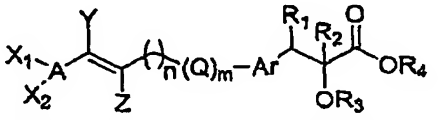
Leptin resistance is a condition wherein the target cells are unable to respond to leptin signal. This may give rise to obesity due to excess food intake and reduced energy

expenditure and cause impaired glucose tolerance, type 2 diabetes, cardiovascular diseases and such other interrelated complications. Kallen *et al* (*Proc. Natl. Acad. Sci.* (1996) 93, 5793-5796) have reported that insulin sensitizers which perhaps due to the PPAR agonist expression lower plasma leptin concentrations. However, it has been recently disclosed that compounds having insulin sensitizing property also possess leptin sensitization activity. They lower the circulating plasma leptin concentrations by improving the target cell response to leptin (WO 98/02159).

Fibrates are a class of drugs which may lower serum triglycerides, lower LDL-C, shift the LDL particle size from the more atherogenic small dense to normal dense LDL-C and increase the HDL-C. Experimental evidence indicate that the effects of fibrates on serum lipids are mediated through activation of PPAR-α *(Curr. Pharm. Des., 1-14, 3(1), 1997)*. Activation of PPAR-α results in transcription of enzymes that increases fatty acids catabolism and decrease denovo fatty acid synthesis in the liver resulting in decreased triglyceride synthesis in the liver resulting in decreased triglyceride synthesis and VLDL-C production. PPAR-α ligands may be useful for the treatment of dyslipidemia and cardiovascular disorders *(Curr.Opin. Lipido., 1999, 10, 245-257)*.

Some of relevant compounds described in the prior art are outlined below:

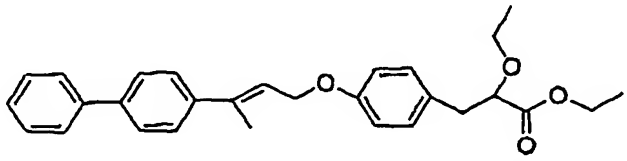
(i) International publication no. WO 01/55085 A1 disclose the compound of general formula (IV)



(IV)

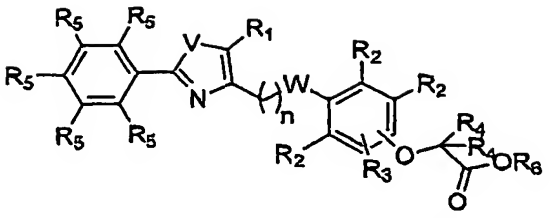
where all symbols are as defined in the PCT publication.

An example of the above compounds as shown in formula (IVb)



(IVa)

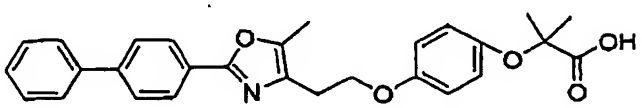
(ii) International publication no. WO 01/16120 A1 disclose the compound of general formula (V)



(V)

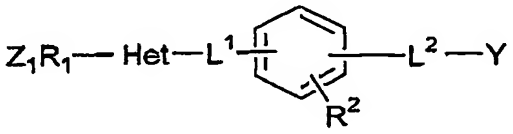
where all symbols are as defined in the PCT publication.

An example of the above compounds as shown in formula (Va)



(Va)

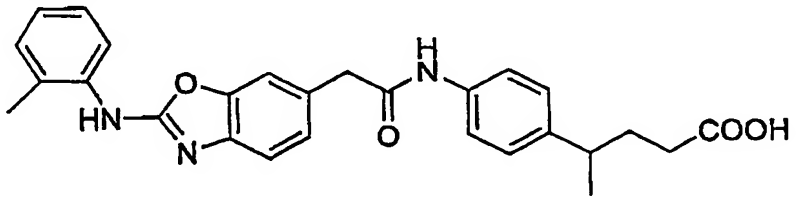
(iii) International publication No. WO 00/49005 disclose the compounds of general formula (VI)



(VI)

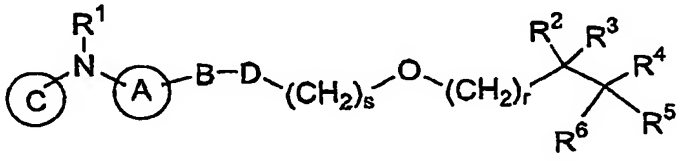
where all symbols are as defined in the PCT publication.

An example of these compounds is shown in formula (VIa)



(VIa)

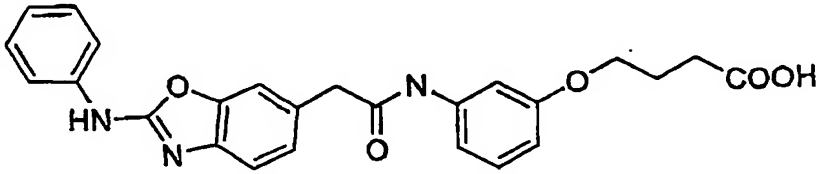
(iv) International publication No. WO 00/05223 disclose the compounds of general formula (X)



(X)

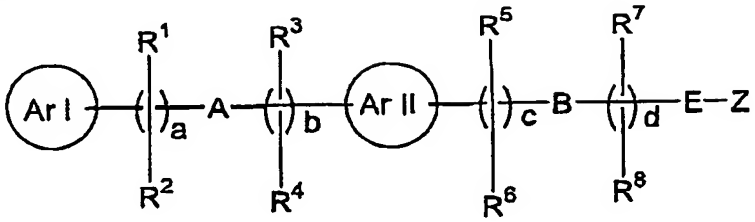
where all symbols are as defined earlier.

An example of these compounds is shown in formula (Xa)



(Xa)

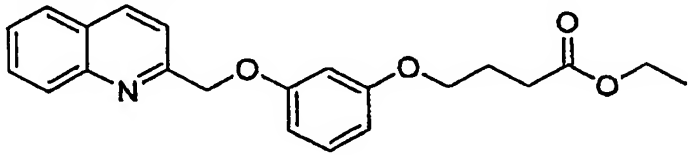
(v) International publication No. WO 00/64888 disclose the compounds of general formula (XI)



(XI)

where all symbols are as defined earlier.

An example of these compounds is shown in formula (XIa)



(XIa)

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (PCT Publication nos. WO 99/16758, WO 99/19313, WO 99/08501, WO97/36579, WO 97/25042, WO 95/17394, WO 96/04260, WO 95/03038, WO 94/13650, WO 94/01420 etc.

Summary of the Invention

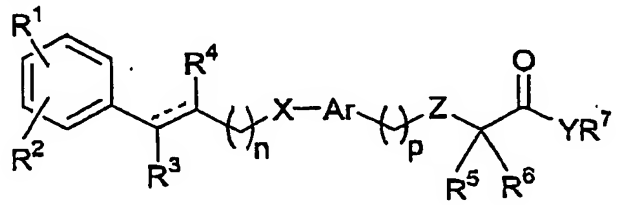
The objective of the present invention is to provide a novel compounds of the general formula (I), as defined above, having PPAR agonist activity with reduced toxicities associated with PPAR γ activation for reducing lipid levels, lowering cholesterol and reducing body weight and reducing blood glucose with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetic complications thereof, and the invention also provides compounds for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of hypertension. We focused our research to develop new compounds with better efficacy, potency, lower toxicity and effective in the treatment of the above mentioned diseases. Effort in this direction has led to compounds having general formula (I), as defined above.

The present invention provides novel compounds of the general formula (I), as defined above.

A process for the preparation of compounds of formula (I), as defined above.

Yet another aspect of the present invention is to provide a pharmaceutical composition, containing the compounds of the general formula (I) as defined above and one or more HMG CoA reductase inhibitors; cholesterol absorption inhibitors; antiobesity drugs; lipoprotein disorder treatment drugs; hypoglycemic agents: insulin; biguanides; sulfonylureas; thiazolidinediones; dual PPARα and γ or a mixture thereof in combination with the usual pharmaceutically employed carriers, diluents and the like.

In accomplishing the above mentioned objects, there has been provided according to one aspect of the present invention, compounds of formula I



(I)

wherein:

R^1 and R^2 may be same or different and independently represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted group selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroarylcarbonyl, aryloxy, aralkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, heteroarylcarbonylamino, heteroaryl, heterocyclyl, heteroaralkoxy, heteroaryloxy, fluorenylmethoxycarbonyl (Fmoc), fluorenylmethoxycarbonylamino (N-Fmoc), -OSO_2R^8, -$OCONR^8R^9$, NR^8COOR^9, -NR^8COR^9, -NR^8R^9, -$NR^8SO_2R^9$, $NR^8CONR^9R^{10}$, -$NR^8CSNR^8R^9$, -SO_2R^8, -SOR^8, -SR^8, -$SO_2NR^8R^9$, -SO_2OR^8, $CONR^8R^9$, $COOR^9$, COR^9, wherein R^8, R^9 and R^{10} may be same or different and independently represent hydrogen, alkyl, aryl, aralkyl, aryloxy or heteroaryl or R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring, which may optionally contain up to 3 heteroatoms selected from N, S, or O and may be unsubstituted or have up to 4 substituents which may be identical or different.

R^3 and R^4 may be same or different and independently represent represent hydrogen, halogen, optionally substituted alkyl, cycloalkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group. 'n' and 'p' represent 0-6.

X represents O, S, NR where R represents hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, alkanoyl, or aroyl.

Ar represents optionally substituted, divalent, single or fused aromatic, heteroaromatic or heterocyclic group.

Z represents O, S, NR, where R represents hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, alkanoyl, or aroyl.

R^5 and R^6 may be same or different and independently represent hydrogen, hydroxy, halogen or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, aryl, aralkyl or heteroaralkyl groups. R^5 and R^6 together may form a 5 or 6 membered cyclic rings, which may contain one or two hetero atoms selected from O, S or N.

Y represents oxygen or NR^{11} where R^{11} represent hydrogen, optionally substituted groups selected from alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl or heteroaryl.

R^7 and R^{11} together may also form a 5 or 6 membered cyclic ring, which may contain one or two hetero atoms selected from O, S or N.

'----' represents a bond or no bond.

According to an embodiment of the present invention, there is provided a compound of formula (I) wherein:

R^1 and R^2 may be same or different and independently represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted alkyl, alkoxy, aryl, aralkyl, aralkoxy, heteroaryl, heteroaralkoxy, $-OSO_2R^8$, $-SO_2R^8$, NR^8R^9;

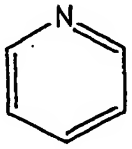
R^3 and R^4 may be same or different and independently represent hydrogen, halogen, optionally substituted alkyl, aralkyl;

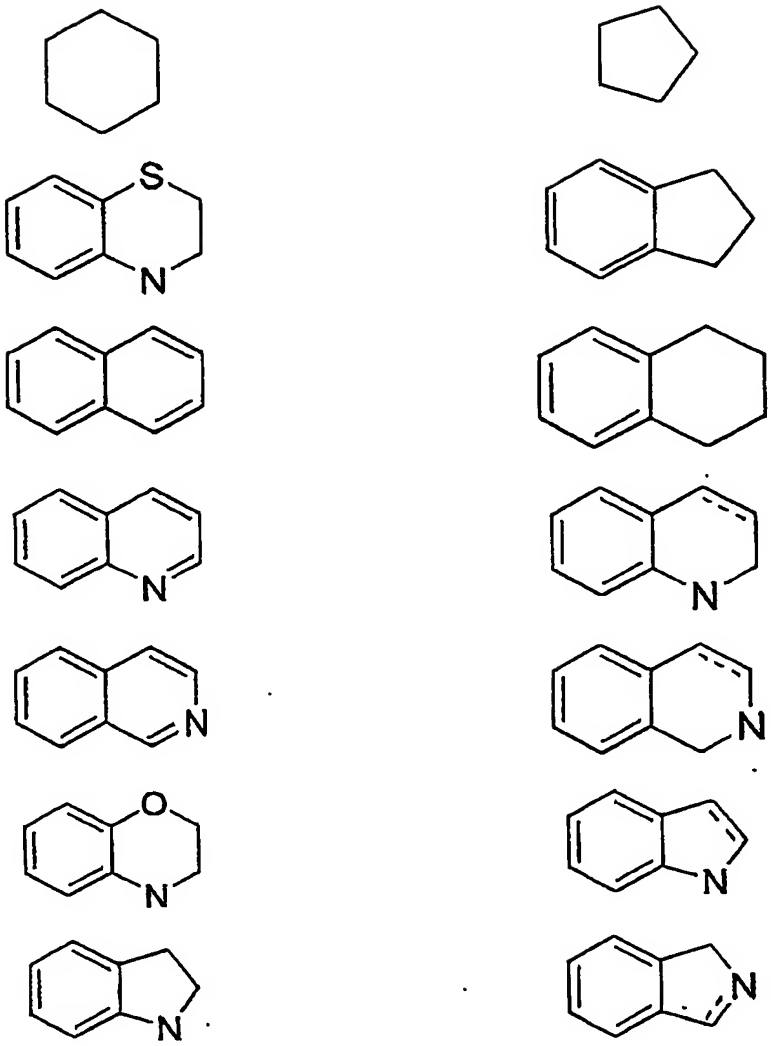
R^5 and R^6 may be same or different and independently represent hydrogen, hydroxy, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered aromatic or non aromatic cyclic ring system optionally containing 1 or 2 heteroatoms selected from O, S or N;

R^7 and R^{11} may for a cyclic ring system selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolinyl, diazolinyl and the like.

According to another embodiment of the present invention, there is provided a compound of formula (I) wherein:

R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring selected from:





According to yet another embodiment of the present invention, there is provided a compound of formula (I) wherein:

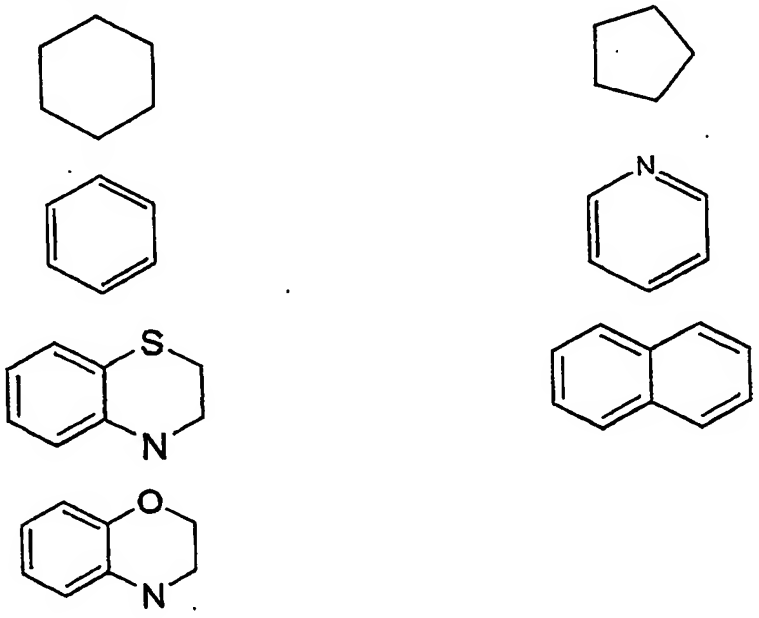
R^1 and R^2 may be same or different and independently represent hydrogen, halogen, nitro, amino, hydroxy or optionally substituted alkyl, aryl, aralkyl, aralkoxy, heteroaryl, heteroaralkoxy, $-OSO_2R^8$;

R^3 and R^4 may be same or different and independently represent hydrogen, optionally substituted alkyl;

R^5 and R^6 may be same or different and independently represent hydrogen, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered saturated cyclic ring system;

According to still another embodiment of the present invention, there is provided a compound of formula (I) wherein:

R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring selected from:



R^3 and R^4 may be same or different and independently represent hydrogen, optionally substituted alkyl;

R^5 and R^6 may be same or different and independently represent hydrogen, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered saturated cyclic ring system;

According to yet another embodiment of the present invention, there is provided a compound of formula (I) wherein:

R^1 is selected from $-OSO_2CH_3$, halogen, alkyl optionally substituted phenyl wherein the substituent is selected from alkyl or halogen

R^2, R^3, R^4, R^5, R^6 and R^7 may be same or different and independently represent hydrogen, methyl, ethyl or propyl

'Ar' represents optionally substituted phenyl wherein the substituent is C_{1-10}alkyl

X, Y and Z independently represent oxygen

n and p independently represent 0 or 1

According to still another embodiment of the present invention, there is provided a compound of formula (I) wherein:

R^1 is selected from optionally substituted phenyl wherein the substituent is selected from halogen

R^2, R^3, R^4, R^5, R^6 and R^7 may be same or different and independently represent hydrogen, methyl, ethyl or propyl

'Ar' represents optionally substituted phenyl wherein the substituent is C_{1-10}alkyl

X, Y and Z independently represent oxygen

n and p independently represent 0 or 1

A preferred embodiment of the present inventions includes compound of formula I selected from:

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(3-biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionioc

Ethyl 2-{4-[3-(4'-fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butyric acid

Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butanote

2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionic acid

Ethyl 2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionate

2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butyric acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butanoate

2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionate

1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid
1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid ethyl ester.

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionate

2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionate

2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butyric acid
Ethyl 2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butanoate

2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionate

2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butyric acid
Ethyl 2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butanoic

A still more preferred embodiment of the present inventions includes compound of formula I selected from:

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionate

2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionate

A yet another preferred embodiment of the present inventions includes compound of formula I selected from:

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionioc

Ethyl 2-{4-[3-(4'-fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butyric acid

Ethyl 2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butanote

2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionate

A yet another preferred embodiment of the present inventions includes compound of formula I selected from:

2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butyric acid

Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butanote

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butyric acid

Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butanoate

1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentanc carboxylic acid
1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid ethyl ester.

A yet another preferred embodiment of the present inventions includes compound of formula I selected from:
2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionate

A yet another preferred embodiment of the present inventions includes compound of formula I selected from:
2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionate

A yet another preferred embodiment of the present inventions includes compound of formula I selected from:
2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butyric acid
Ethyl 2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butanote

2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionate

Detailed Description of the Invention and Embodiments

The novel compounds of the general formula (I), as defined above, have PPAR agonist activity with reduced toxicities associated with PPAR γ activation for reducing lipid levels, lowering cholesterol and reducing body weight and reducing blood glucose with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetic complications thereof, and the invention also provides compounds for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of hypertension. We focused our research to develop new compounds with better efficacy, potency, lower toxicity and effective in the treatment of the above mentioned diseases

The compounds of the present invention are administered in dosages effective to agonize peroxisome proliferators activated receptor where such treatment is needed, as, for example, in the prevention or treatment of diabetes, hypertension, coronary heart disease, atherosclerosis, stroke, peripheral vascular diseases, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, retinopathy, arteriosclerosis, xanthoma and related disorders. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic

salts of the compounds of this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base. Representative salts include the following: Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; N,N'-diacetylethylenediamine, betaine, caffeine, 2-diethylaminoethanol, 2-dimethylaminoethanol, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, hydrabamine, isopropylamine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, diethanolamine, meglumine, ethylenediamine, N,N'-diphenylethylenediamine, N,N'-dibenzylethylenediamine, N-benzyl phenylethylamine, choline, choline hydroxide, dicyclohexylamine, metformin, benzylamine, phenylethylamine, dialkylamine, trialkylamine, thiamine, aminopyrimidine, aminopyridine, purine, spermidine; alkylphenylamine, glycinol, phenyl glycinol; glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, serine, threonine, phenylalanine; unnatural amino acids; D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts; sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, or ketoglutarates.

The compounds of the present invention, may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such pro drugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The terms "individual," "subject," "host," and "patient" refer to any subject for whom diagnosis, treatment, or therapy is desired. In one embodiment, the individual,

subject, host, or patient is a human. Other subjects may include, but are not limited to, animals including but not limited to, cattle, sheep, horses, dogs, cats, guinea pigs, rabbits, rats, primates, opossums and mice. Other subjects include species of bacteria, phages, cell cultures, viruses, plants and other eucaryotes, prokaryotes and unclassified organisms.

The terms "treatment," "treating," "treat," and the like are used herein to refer generally to obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a subject, particularly a human, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to the disease or symptom, but has not yet been diagnosed as having it; (b) inhibiting the disease symptom, i.e., arresting its development; or (c) relieving the disease symptom, i.e., causing regression of the disease or symptom.

The term "therapeutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or patient that is being sought.

The groups defined for R, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are defined as below:

'Alkyl' group is linear or branched (C_1-C_{10})alkyl group. Exemplary alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, hexyl, heptyl, octyl and the like.

'Cycloalkyl' group is (C_3-C_{10})cycloalkyl group. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

'Cycloalkylalkyl' group is (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl group, where cycloalkyl and alkyl groups are as defined earlier. Exemplary cycloalkylalkyl groups include cyclopropyl-methyl, cyclobutyl-methyl, cyclopentyl-methyl, cyclohexyl-methyl and the like.

'Alkoxy' is (C_1-C_{10})alkyl-O-, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkyl groups include methoxy, ethoxy, propyloxy, butyloxy, iso-propyloxy and the like.

'Cycloalkoxy' is (C_3-C_{10})cycloalkoxy group. Exemplary cycloalkoxy groups include cyclopropoxy, cyclobutoxy, cyclopentoxy, cyclohexoxy and the like.

'Alkanoyl' is H-CO- or (C_1-C_{10})alkyl-CO-, where (C_1-C_{10})alkyl group is as defined above. Exemplary acyl groups include acetyl, propanoyl, butanoyl, pentanoyl, benzoyl and the like.

'Aralkanoyl' is aryl-alkanoyl group, where aryl and alkanoyl groups are as defined earlier. The exemplary aralkanoyl groups include phenylpropanoyl, phenylbutanoyl, phenylpentanoyl and the like.

'Aryl' is monocylic or multicyclic ring system of about 6 to 14 carbon atoms. Exemplary groups include phenyl, naphthyl and like.

'Aryloxy' is aryl-O- group, where aryl group is as defined above. Exemplary aryloxy groups include phenoxy, naphthyloxy and the like.

'Aroyl' is aryl-CO- group. Exemplary aroyl groups include benzoyl, 1-naphthoyl and the like.

'Aralkyl' is aryl-(C_1-C_{10})alkyl group, where in aryl and (C_1-C_{10})alkyl groups are as defined above. Exemplary aralkyl groups include benzyl, 2-phenethyl and the like.

'Aralkoxy' is aralkyl-O- group, wherein the aralkyl group as defined above. Exemplary aralkoxy groups include benzyloxy, 2-phenethyloxy and the like.

'Heterocyclyl' is a non-aromatic saturated monocyclic or multicyclic ring system of about 5 to about 10 carbon atoms, having at least one hetero atom selected from O, S or N. Exemplary heterocyclyl groups include aziridinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl and the like.

'Heteroaralkoxy' is heteroaralkyl-O-, wherein heteroaralkyl group is as defined above. Exemplary heteroaralkoxy groups include thienylmethyloxy, pyridylmethyloxy and the like.

'Heteroaryloxy' is heteroaryl-O-, wherein heteroaryl group is as defined above. Exemplary beteroaryloxy groups include pyrazinyloxy, isothiazolyloxy, oxazolyloxy, pyrazolyloxy, pyridazinyloxy, phthalazinyloxy, indolyloxy, quinazolinyloxy, pyridyloxy, thienyloxy and the like.

'Heteroaryl' is an aromatic monocyclic or multicyclic ring system of about 5 to about 10 carbon atoms, having at least one heteroatom selected from O, S or N. Exemplary heteroaryl groups include as pyrazinyl, isothiazolyl, oxazolyl, pyrazolyl, pyrrolyl, pyridazinyl, thienopyrimidyl, furyl, indolyl, isoindolyl, 1,3-benzodioxole, 1,3-benzoxathiole, quinazolinyl, pyridyl, thiophenyl and the like.

'Heteroaralkyl' is heteroaryl-(C_1-C_{10})alkyl group, wherein the heteroaryl and (C_1-C_{10})alkyl groups are as defined above. Exemplary heteroaralkyl groups include thienylmethyl, pyridylmethyl, imidazolylmethyl and the like.

'Alkylcarbonyl' is (C_1-C_{10})alkyl-CO-, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkylcarbonyl groups include methylcarbonyl, ethylcarbonyl, propylcarbonyl and the like.

'Alkylcarbonyloxy' is (C_1-C_{10})alkyl-CO-O, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkylcarbonyloxy groups include methylcarbonyloxy, ethylcarbonyloxy, propylcarbonyloxy and the like.

'Alkoxycarbonyl' is (C_1-C_{10})alkyl-O-CO-, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl and the like.

'Alkoxycarbonylamino' is (C_1-C_{10})alkyl-O-CO-amino, wherein (C_1-C_{10})alkyl group is as defined above. Exemplary alkoxycarbonyl groups include methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino and the like.

'Arylcarbonyl' is aryl-CO-, wherein aryl group is as defined above. Exemplary arylcarbonyl groups include phenylcarbonyl, naphthylcarbonyl and the like.

'Aryloxycarbonyl' is aryl-O-CO-, wherein aryl group is as defined above. Exemplary aryloxycarbonyl groups include phenoxycarbonyl, naphthyloxycarbonyl and the like.

'Aryloxycarbonylamino' is aryl-O-CO-amino, wherein aryl group is as defined above. Exemplary aryloxycarbonyl groups include phenoxycarbonylamino, naphthyloxycarbonylamino and the like.

'Aralkoxycarbonyl' is aryl-(C_1-C_{10})alkoxy-CO-, where aryl and (C_1-C_{10})alkoxy are as defined above. Exemplary aralkoxycarbonyl groups include benzyloxycarbonyl, 2-phenethyloxycarbonyl and the like.

'Aralkoxycarbonylamino' is aryl-(C_1-C_{10})alkoxy-CO-amino, where aryl and (C_1-C_{10})alkoxy are as defined above. Exemplary aralkoxycarbonyl groups include benzyloxycarbonylamino, 2-phenethyloxycarbonylamino and the like.

'Heteroarylcarbonyl' is heteroaryl-CO-, wherein heteroaryl is as defined above. Exemplary heteroarylcarbonyl groups include pyrazinylcarbonyl, isothiazolylcarbonyl, oxazolylcarbonyl, pyrazolylcarbonyl, pyrrolylcarbonyl, pyridazinylcarbonyl, indolylcarbonyl and the like.

'Heteroarylcarbonylamino' is heteroaryl-CO-amino, wherein heteroaryl is as defined above. Exemplary heteroarylcarbonylamino groups include pyrazinylcarbonylamino, isothiazolylcarbonylamino, oxazolylcarbonylamino, pyrazolylcarbonylamino, pyrrolylcarbonylamino, pyridazinylcarbonylamino, indolylcarbonylamino and the like.

'Ar' may be selected from optionally substituted groups selected from divalent phenylene, naphthylene, pyridyl, quinolinyl, benzofuryl, dihydrobenzofuryl, benzopyranyl, dihydrobenzopyranyl, indolyl, indolinyl, azaindolyl, azaindolinyl, pyrazolyl, benzothiazolyl, benzoxazolyl and the like. The substituents on the group represented by Ar may be selected from linear or branched optionally halogenated (C_1-C_{10})alkyl, optionally halogenated (C_1-C_{10})alkoxy, halogen, acyl, amino, acylamino, thio or carboxylic or sulfonic acids and their derivatives.

It is more preferred that 'Ar' represent optionally substituted divalent, phenylene, naphthylene, benzofuryl, indolyl, indolinyl, quinolinyl, azaindolyl, azaindolinyl, benzothiazolyl or benzoxazolyl groups.

It is still more preferred that 'Ar' is represented by divalent phenylene, naphthylene or benzofuryl, which may be unsubstituted or substituted by alkyl, haloalkyl, methoxy or haloalkoxy groups.

The substituents on the fused rings formed by R^1 and R^2 may be selected from (C_1-C_{10})alkyl, halogen, hydroxy, halo(C_1-C_{10})alkyl, nitro, amino, cyano, oxo, or thioxo.

The substituents on R^1 and R^2 are selected from halogen, hydroxy, nitro, amino, oxo, thioxo, optionally substituted groups selected from (C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})alkoxy, aryl, aralkyl, (C_1-C_{10})alkylsulfonyl, (C_1-C_{10})alkylsulinyl, (C_1-C_{10})alkylsulfanyl, (C_1-C_{10})alkylsulfonyloxy, (C_1-C_{10})alkylsulinyloxy, (C_1-C_{10})alkylsulfanyloxy. The substituents are selected from halogen, hydroxyl, nitro, amino, cyano or (C_1-C_{10})alkyl.

Cyclic rings formed by R^5 and R^6 together may form a 5 or 6 membered cyclic rings selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like; pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl and the like.

The substituents on R, R^3, R^4, R^7 and R^{11} may be selected from halogen, nitro, amino, hydroxy, (C_1-C_{10})alkyl, oxo, aralkyl

The substitutents on R^5 , R^6 and R^7 may be selected from halogen, hydroxy, nitro, (C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})alkoxy, aryl, aralkyl, aralkoxy(C_1-C_{10})alkyl, heterocyclyl, heteroaryl, amino.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

All publications and patents mentioned herein are incorporated herein by reference for the purpose of describing and disclosing, for example, the constructs and methodologies that are described in the publications, which might be used in connection with the presently described invention. The publications discussed above and throughout the text are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention.

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, constructs, and reagents described herein and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 0.1 to 50%, preferably 1 to 20% by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active ingredient will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the active ingredient can be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavourants, sweeteners, excipients and the like. For parenteral administration, the active ingredient can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example,

solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds. Aqueous solutions with the active ingredient dissolved in polyhydroxylated castor oil may also be used for injectable solutions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For nasal administration, the preparation may contain the active ingredient of the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, such as propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin or preservatives such as parabenes. .

Tablets, dragees or capsules having talc and / or a carbohydrate carried binder or the like are particularly suitable for any oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and / or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician, veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably 0.01 to 10 mg/kg/day, and most preferably 0.1 to 5.0 mg/kg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, preferably, from about 1 mg to about 100 mg of active ingredient. Intravenously, the most preferred doses will range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be

administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as 'carrier' materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or betalactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

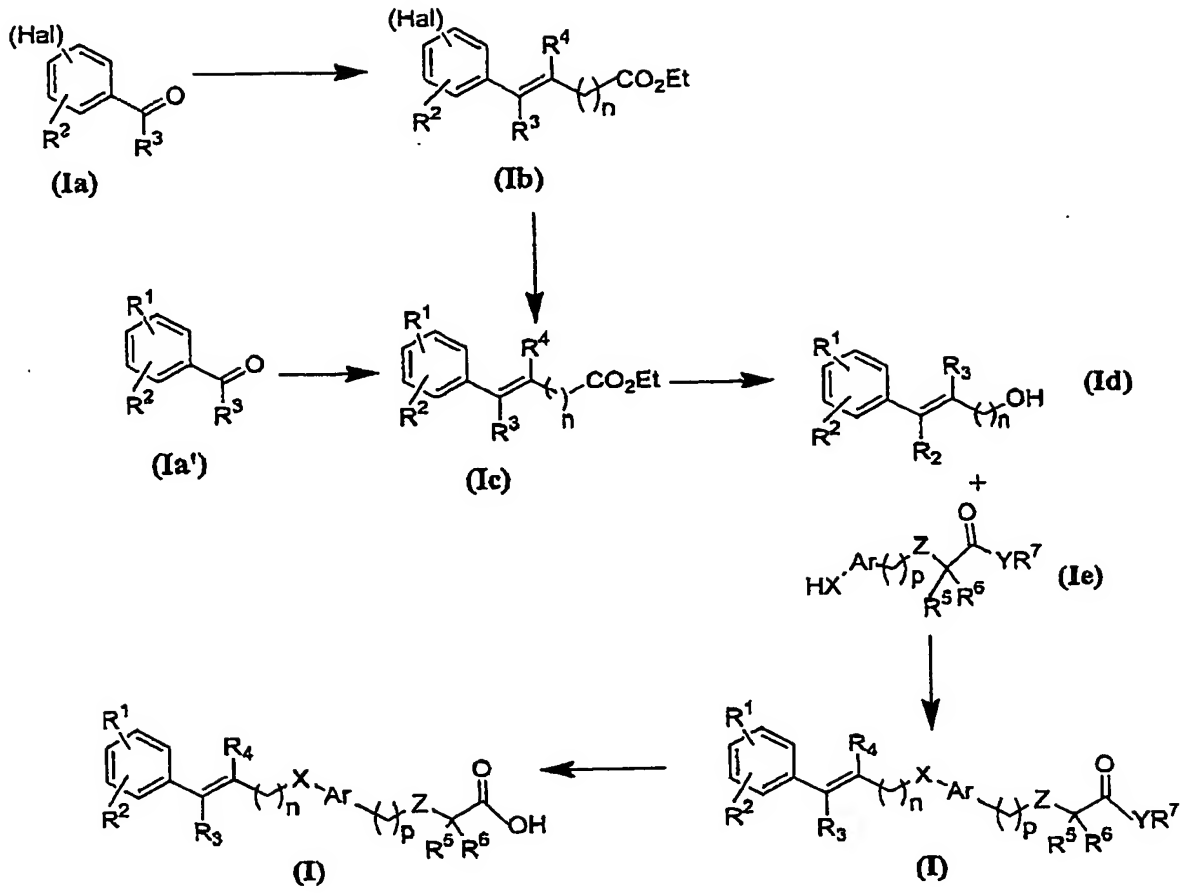
Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone,

pyran copolYmer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polYmers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolYmers of polyactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy · butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolYmers of hydrogels.

The compounds of formula 1 can generally be prepared, for example in the course of a convergent synthesis, by linkage of two or more fragments which can be derived retrosynthetically from the formula 1. in the preparation of compounds of formul 1, it may be generally necessary in the course of synthesis temporarily block functional groups which could lead to undesired reactions or side reactions in a synthetic step by protective group suited to the synthesis problem and known to the person skilled in the art. The method of fragment coupling is not restricted to the following examples, but is generally applicable for synthesis of compounds of formula 1.

The novel compounds of the present invention were prepared according to the procedure of the following schemes and examples, using appropriate materials and are further exemplified by the following specific examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

The following Schemes and Examples describe procedures for making representative compounds of the present invention. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein.Scheme 1: The compounds of general formula (I), where p represents 1 and all other symbols are as defined earlier, may be prepared by the process as shown in Scheme-I below:



Scheme-1

The compound of formula (Ia) is converted to a compound of formula (Ib) where 'Hal' represents halogen atom such as bromine or iodine, and R^2 represents hydrogen atom, in a Witting-Horner reaction manner, by using phosphono acetate compounds selected from substituted phosphone acetate compounds such as triethyl phosphono acetates, trimethylphosphono acetate, Ph_3P^+-CH_2^--CO_2Et and the like. The base used in the reaction may be selected from sodium hydride, potassium tertiary butoxide, potassium hydroxide, sodium methoxide, sodium ethoxide and the like. The solvent used in the reaction is selected from alcohol selected from methanol, ethanol, propanol, isopropanol and the like or mixtures thereof, tetrahydrofuran, ether, dioxane, dimethoxyethane and the like. The temperature of the reaction is maintained in the range of 0 to 10 °C, preferably 0 °C. The duration of the reaction is maintained in the range of 10 to 24 h, preferably in the range of 12 to 18 h.

The compound of formula (Ib), where 'Hal' represents halogen atom such as bromine or iodine, and R^2 represents hydrogen atom, is converted to a compound of formula (Ic), where R^1 represent aryl group and R^2 represents hydrogen atom, in a Suzuki coupling reaction manner, by using aryl boronic acid with palladium catalyst like $Pd(PPh_3)_4$, $PdCl_2$, $Pd(dba)_2$ and the like. The solvent used in the reaction is selected from terahydrofuran, dioxane, acetonitrile, dimethylether, diethylether, dimethylformamide and the like. The reaction may be carried out at a reflux temperature of the solvent used. The duration of the reaction may be in the range of 15 to 28 h, preferably in the range of 15 to 24 h.

The compound of formula (Ic), is prepared from compound of formula (Ia'), where R^1 and R^2 are as defined in the formula (I), by using substituted phosphone acetate compounds selected from triethyl phosphono acetates, trimethylphosphono acetate, Ph_3P^+-CH_2^--CO_2Et and the like.

The reduction of the compound of formula (Ic) to a compound of formula (Id) may be carried out in the presence of a reducing agent selected from DIBAL-H, AlH_3, lithium aluminium (LAH) and the like. The solvent used in the reaction may be selected from toluene, tetrahydrofuran, ether, dioxane, dimethoxyethane and the like. The temperature of the reaction may be in the range of -90 to -25 °C, preferably in the range of -80 to -60 °C. The duration of the reaction may in the range of 0.5 h to 2 h, preferably in the range of 0.5 to 1 h. The temperature and duration of the reaction can be decreased in the presence of AlH_3.

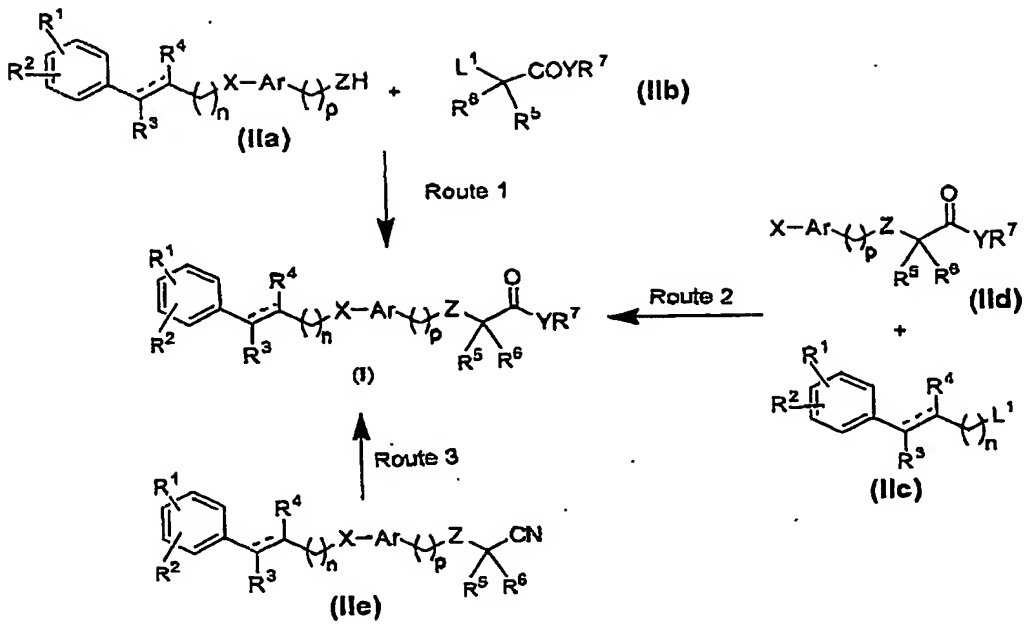
The coupling of a compound of formula (Id) with a compound of formula (Ic), where p represents 1, Y represents O or S, (Mitsinobu reaction) to obtain a compound of formula (I), where p represents 1, Y represents O or S, R^7 represents all the groups as defined earlier, except hydrogen atom and all other symbols are as defined earlier, by using PPh_3, DIAD, DEAD and the like. The solvent used in the reaction is selected from tetrahydrofuran, toluene, benzene and the like. The reaction temperature may be in the range of 20 to 40 °C, preferably at room temperature. The duration of the reaction may be in the range of 40 to 80 h, preferably in the range of 40 to 72 h.

The compound of general formula (I) where R^7 represents hydrogen atom, Y represents O or S, p represents 1 and all other symbols are as defined earlier, may be prepared from a compound of formula (I) where R^7 represents all groups defined earlier except hydrogen, Y represents O or S, p represents 1 and all other symbols are as defined earlier, by hydrolysis using conventional methods. The reaction may be carried out in the

presence of a base such as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate and the like. The solvent used may be selected from alcohols such as methanol, ethanol, propanol, isopropanol and the like or mixtures thereof, water, tetrahydrofuran, dioxane, ether and the like or mixtures thereof. The temperature of the reaction may be in the range of 30 to 80 °C, preferably at room temperature. The duration of the reaction may be in the range of 2 to 24 h, preferably 2 to 12 h.

The compound of general formula (I) where Z represents O or S, p represents 1 and R^7 represents hydrogen or lower alkyl group may be converted to compound of formula (I), where Y represents NR^{11} by reacting with appropriate amines of the formula NHR^7R^{11}, where R^7 and R^{11} are as defined earlier to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier. Alternatively, the compound of formula (I) where YR^7 represents OH may be converted to acid halide, preferably YR^7 = Cl, by reacting with appropriate reagents such as oxalyl chloride, thionyl chloride and the like, followed by treatment with amines of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier. Alternatively, mixed anhydrides may be prepared from compound of formula (I) where YR^7 represents OH and all other symbols are as defined earlier by treating with acid halides such acetyl chloride, acetyl bromide, pivaloyl chloride, dichlorobenzoyl chloride and the like. The reaction may be carried out in the presence of pyridine, triethylamine, diisopropyl ethylamine and the like. Coupling reagent such as DCC/DMAP DCC/HOBt, EDCI/HOBT, DIC/HOBt, ethylchloroformate, isobutylchloroformate can also be used to activate the acid. The reaction may be carried out in the presence of a solvent such as halogenated hydrocarbon like $CHCl_3$ or CH_2Cl_2; hydrocarbon such as benzene, toluene, xylene and the like.. The reaction may be carried out at a temperature in the range of –40 to 40 °C, preferably at a temperature in the range of 0 to 20 °C. The acid halide or mixed anhydride or activated acid obtained by coupling reagents described above thus prepared may further be treated with appropriate amine of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier, to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier.

Scheme 2: The compounds of general formula (I), where p represents 1 and all other symbols are as defined earlier, may be prepared by the process as shown in Scheme-2:



Scheme-2

Route 1: The reaction of compound of formula (IIa) with compound of formula (IIb) where L^1 is a leaving group such as hydroxy, halogen atom, *p*-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, and where all symbols are as defined earlier, may be carried out in the presence of an aprotic solvent such as THF, DMF, DMSO, DME, toluene, benzene, xylene and the like or mixtures thereof. The reaction may be carried out in the presence of a organic base such as triethylamine, collidine, lutidine and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere that may be maintained by using an inert gas such as nitrogen, helium or argon. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3, $NaNH_2$, n-BuLi, NaH, KH and the like. The reaction temperature may range from 0 to 120 °C, preferably in the range of 25 to 100 °C. The duration of the reaction may range from 1 to 72 h, preferably from 2 to 24 h.

Route 2: The reaction of compound of formula (IIc) with compound of formula (IId), where L^1 represents a leaving group such as hydroxy, halogen atom, *p*-toluenesulfonate, methanesulfonate, trifluoromethanesulfonate and the like, and all other symbols are as defined earlier, may be carried out in the presence of an aprotic solvent such as THF, DMF, DMSO, DME and the like or mixtures thereof. The reaction may be carried out in an inert atmosphere that may be maintained by using an inert gas such as nitrogen, argon,

helium and the like. The reaction may be effected in the presence of a base such as K_2CO_3, Na_2CO_3 or NaH, KH, triethyl amine and the like or mixtures thereof. The reaction temperature may range from 0 to 120 °C, preferably in the range of 25 to 100 °C. The duration of the reaction may range from 1 to 72 h, preferably from 2 to 24 h.

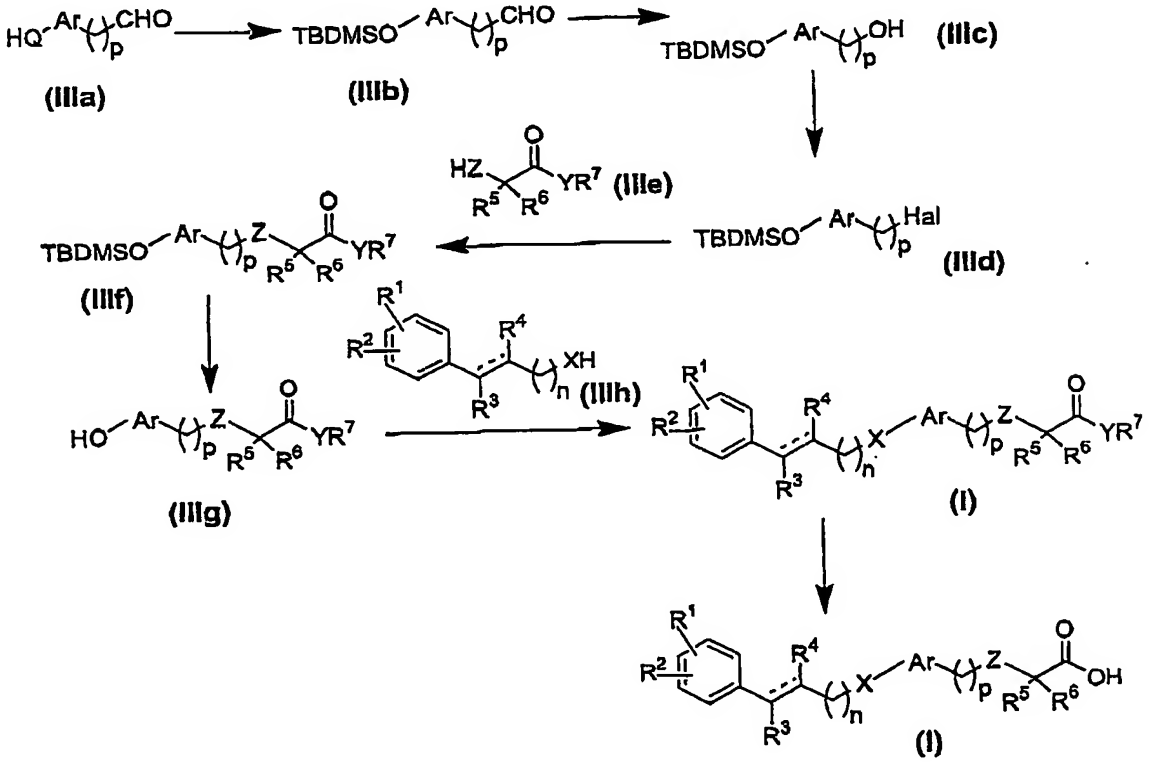
Route 3: The conversion of compound of formula (IIe) to a compound of formula (I), where all symbols are as defined earlier, may be carried out either in the presence of a base or an acid and the selection of a base or an acid is not critical. Any base normally used for hydrolysis of nitrile to an acid may be employed, metal hydroxide such as NaOH or KOH in an aqueous solvent or any acid normally used for hydrolysis of nitrile to ester may be employed such as dry HCl in an excess of alcohol such as methanol, ethanol, propanol, isopropanol and the like. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent used, preferably at a temperature in the range of 25 °C to reflux temperature of the solvent used. The duration of the reaction may range from 0.25 to 48 h.

The compound of general formula (I) where R^7 represents hydrogen atom may be prepared by hydrolysis using conventional methods, a compound of formula (I) where R^7 represents all groups defined earlier except hydrogen. The hydrolysis may be carried out in the presence of a base such as Na_2CO_3, K_2CO_3, NaOH, KOH, LiOH and the like and a suitable solvent such as methanol, ethanol, propanol, isopropoanol, water and the like or mixtures thereof. The reaction may be carried out at a temperature in the range of 20 to 120 °C. The reaction time may range from 2 to 48 h, preferably from 2 to 12 h.

The compound of general formula (I) where Z represents oxygen and R^7 represents hydrogen or lower alkyl group may be converted to compound of formula (I), where Y represents NR^{11} by reacting with appropriate amines of the formula NHR^7R^{11}, where R^7 and R^{11} are as defined earlier to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier. Alternatively, the compound of formula (I) where YR^7 represents OH may be converted to acid halide, preferably YR^7 = Cl, by reacting with appropriate reagents such as oxalyl chloride, thionyl chloride and the like, followed by treatment with amines of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier. Alternatively, mixed anhydrides may be prepared from compound of formula (I) where YR^7 represents OH and all other symbols are as defined earlier by treating with acid halides such acetyl chloride, acetyl bromide, pivaloyl chloride, dichlorobenzoyl chloride and the like. The reaction may be carried out in the presence of

pyridine, triethylamine, diisopropyl ethylamine and the like. Coupling reagent such as DCC/DMAP DCC/HOBt, EDCI/HOBT, DIC/HOBt, ethylchloroformate, isobutylchloroformate can also be used to activate the acid. The reaction may be carried out in the presence of a solvent such as halogenated hydrocarbon like $CHCl_3$ or CH_2Cl_2; hydrocarbon such as benzene, toluene, xylene and the like.. The reaction may be carried out at a temperature in the range of –40 to 40 °C, preferably at a temperature in the range of 0 to 20 °C. The acid halide or mixed anhydride or activated acid obtained by coupling reagents described above thus prepared may further be treated with appropriate amine of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier, to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier.

Scheme 3: The compounds of general formula (I), where p represents 2-6 and all other symbols are as defined earlier may be prepared by the process as shown in Scheme-3 below:



Scheme 3

The compound of formula (IIIa) is converted to a compound of formula (IIIb) by reacting with TBDMS-Hal, where 'Hal' represents halogen atom. $(CH_3)_3Si$-Hal, Ph_3C-Hal may also be used. The base used in the reaction may be selected from triethylamine, Na_2CO_3, K_2CO_3 and the like. The solvent used in the reaction may be selected from

dichloromethane, tetrahydrofuran, chloroform, dimethylether, diethylether, dioxane, benzene, toluene or mixtures thereof. The temperature of the reaction may be in the range of 0 °C to room temperature. The duration of the reaction may from 8 to 20 h, preferably 8 to 12 h.

The compound of formula (IIIb) is converted to a compound of formula (IIIc) by using $NaBH_4$. The reaction may be carried out in the presence of an alcohol such as methanol, ethanol, proanol, isopropanol and the like. The reaction may be carried out at room temperature for a duration in the range of 1 to 4 h, preferably 1 to 2 h.

The compound of formula (IIIc) is converted to a compound of formula (IIId) in the presence of $C(Hal)_4$, where 'Hal' represents halogen atom. The reaction may be carried out in the presence of PPh_3. The solvent used in the reaction may be selected from dichloromethane, tetrahydrofuran, chloroform, dimethylether, diethylether, dioxane, benzene, toluene or mixtures thereof. The reaction may be carried out at room temperature. The duration of the reaction may be in the range of 0.5 to 2 h, preferably 0.5 to 1 h.

The compound of formula (IIId) is reacted with the compound of formula (IIIe) to obtain a compound of formula (IIIf). The reaction may be carried out in the presence of a base such as NaH, KH, sodium amide, potassium tertiary butoxide etc. The solvent used in the reaction may be selected from DMSO, THF, toluene, benzene and the like or mixtures thereof. The duration of the reaction may be in the range of 50 to 90 °C, preferably in the range of 60 to 80 °C. The duration of the reaction may vary in the range of 8 to 15 h, preferably 8 to 12 h.

The deprotection of compound of formula (IIIf) to obtain a compound of formula (IIIg) may be carried out by using tetrabutylammoniumfluoride (TBAF). The reaction may be carried in the presence of suitable solvent such as water, THF, dioxane, dichloromethane, chloroform, methanol, ethanol etc. or mixtures thereof. The reaction may be carried out at a temperature in the range of 20 to 40 °C, preferably at room temperature. The reaction time may range from 1 to 6 h, preferably from 1 to 4 h.

The compound of formula (IIIg) is converted to a compound of formula (I), where Y represents O or S, R^7 represents all groups as defined earlier but not hydrogen. The reaction may be carried out by using PPh_3, diisopropyl azadicarboxylate (DIAD), diethyl azadicarboxylate (DEAD) and the like. The solvent used in the reaction is selected from tetrahydrofuran, toluene, benzene and the like. The reaction temperature may be in the

range of 20 to 40 °C, preferably at room temperature. The duration of the reaction may be in the range of 40 to 80 h, preferably in the range of 40 to 72 h.

The compound of general formula (I) where R^7 represents hydrogen atom, Y represents O or S, p represents 1 and all other symbols are as defined earlier, may be prepared from a compound of formula (I) where R^7 represents all groups defined earlier except hydrogen, Y represents O or S, p represents 1 and all other symbols are as defined earlier, by hydrolysis using conventional methods. The reaction may be carried out in the presence of a base such as sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate and the like. The solvent used may be selected from alcohols such as methanol, ethanol, propanol, isopropanol and the like or mixtures thereof, water, tetrahydrofuran, dioxane, ether and the like or mixtures thereof. The temperature of the reaction may be in the range of 30 to 80 °C, preferably at room temperature. The duration of the reaction may be in the range of 2 to 24 h, preferably 2 to 12 h.

It is appreciated that in any of the above-mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are tertiarybutyldimethylsilyl, methoxymethyl, triphenyl methyl, benzyloxycarbonyl, tetrahydropyran(THP) etc, to protect hydroxyl or phenolic hydroxy group; N-tert-butoxycarbonyl (N-Boc), N-benzyloxycarbonyl (N-Cbz), N-9-fluorenyl methoxy carbonyl (-N-FMOC), benzophenoneimine, propargyloxy carbonyl (POC) etc, for protection of amino or anilino group, acetal protection for aldehyde, ketal protection for ketone and the like. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The compounds of the present invention can be used for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, nephropathy. The compounds of general formula (I) are also useful for the treatment / prophylaxis of insulin resistance (type II diabetes), leptin resistance, impaired glucose tolerance, dyslipidemia, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease, and other cardiovascular disorders.

The compounds of the present invention may also be useful as aldose reductase inhibitors, for improving cognitive functions in dementia, as inflammatory agents, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic

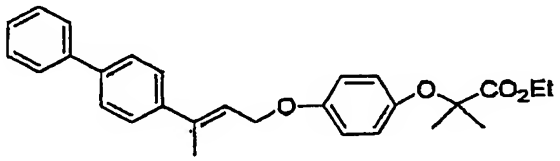
ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, retinopathy, arteriosclerosis, xanthoma and for the treatment of cancer.

The compounds of the present invention are useful in the treatment and / or prophylaxis of the above said diseases in combination / concomittant with one or more HMG CoA reductase inhibitors; cholesterol absorption inhibitors; antiobesity drugs; lipoprotein disorder treatment drugs; hypoglycemic agents: insulin; biguanides; sulfonylureas; thiazolidinediones; dual PPARα and γ or a mixture thereof. The compounds of the present invention in combination with HMG CoA reductase inhibitors, cholesterol absorption inhibitors, antiobesity drugs, hypoglycemic agents can be administered together or within such a period to act synergistically.

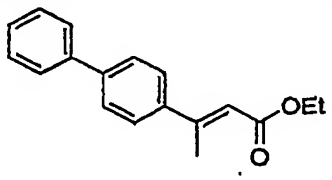
The invention is explained in detail in the examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Example 1:

Ethyl 2-[4-(3-biphenyl-4-yl-but-2-enyloxy)-phenoxy]-2-methyl-propanoic acid



Step (i): Preparation of 3-biphenyl-4-yl-but-2-enoic acid ethyl ester

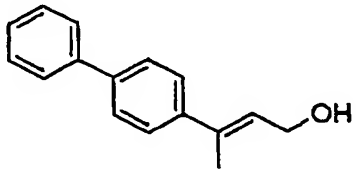


To the 60% NaH (3.06 g, 0.127 mol) suspended in THF (50 mL) was added triethyl phoshonoacetate (12.69 mL, 0.637 mol) drop wise at 0 °C in dry THF (50mL) with stirring under nitrogen atmosphere and the resulting solution was stirred at room temperature for 30 min and 4-acetyl biphenyl (10g, 0.051 mol) in THF (50 mL) was added drop wise at room temperature and the mixture was stirred at room temperature for 18 h, neutralized with 2 N HCl and extracted in to EtOAc. The combined organic layers were washed with water, dried over sodium sulphate and evaporated. The crude 3-biphenyl-4-yl-but-2-enoic

acid ethyl ester was purified over silica gel column by eluting with 5% EtOAc:Pet.ether to give a trans product as white solid (8 g, 59%). Mp. 77-79 °C.

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.70-7.30 (m, 9H), 6.21 (s, 1H), 4.23 (q, J=7.25 Hz, 2H), 2.62 (s, 3H), 1.33 (t, J=7.25 Hz, 3H).

Step (ii): Preparation of 3-biphenyl-4-yl-but-2-ene-1-ol



The 3-biphenyl-4-yl-but-2-enoic acid ethyl ester (8 g), obtained in step (i), was reduced with AlH_3 (prepared from 4.22g of $AlCl_3$ and 3.61g of $LiAlH_4$) in 200 ml of dry THF at −5 °C for 30 min. The reaction mixture was quenched with saturated Na_2SO_4 solution and filtered, washed with EtOAc and combined filtrates were evaporated to give 3-biphenyl-4-yl-but-2-ene-1-ol as a white low melting solid (Yield: 95%). Mp. 117-119 °C.

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.65-7.25 (m, 9H), 6.05 (t, J=6.72 Hz, 1H), 4.40 (d, J=6.72 Hz, 2H), 2.12 (s, 3H).

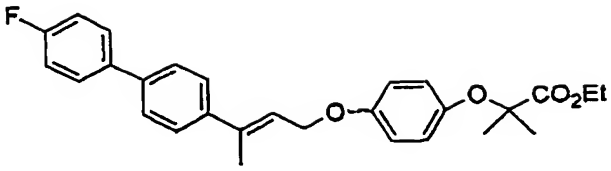
Step (iii): Preparation of 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)-phenoxyl-2-methyl-propanoate

The 3-biphenyl-4-yl-but-2-ene-1-ol (0.455 g), obtained in step (ii), was coupled with the ethyl-4-hydroxy phenoxy-2-methyl-propanoate (Ref: *J. Med. Chem.* 2001, 44, 2061) (0.350 g) by Mitsinobu reaction using diisopropylazodicarboxylate (DIAD) (0.41 g) and PPh_3 (0.532 g) in THF (10 mL) at 25 °C for 48 h. The reaction was worked up by diluting with more of EtOAc and washing with aq.$KHSO_4$ solution and then with water. The dried solvent was evaporated and purified by column chromatography by eluting with 10% EtOAc and pet.ether, to give 52% of the ethyl-2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)-phenoxy]-2-methyl-propanoate as an thick oil.

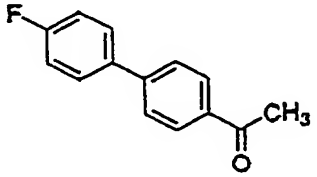
^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.25 (m, 9H), 6.83 (s, 4H), 6.10 (t, J=6.35 Hz, 1H), 4.70 (d, J=6.35 Hz, 2H), 4.23 (q, J=6.84 Hz, 2H), 2.15 (s, 3H), 1.53 (s, 6H), 1.27 (t, J=6.84 Hz, 3H).

Example 2

Ethyl 2-[4-(3-(4'-fluoro-biphenyl-4-yl-but-2-enyloxy)-phenoxy]-2-methyl-propanoate.



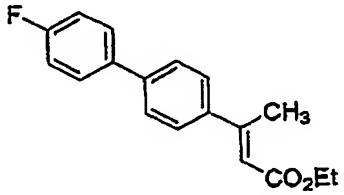
Step (i): Preparation of 4-acetyl-4'-fluoro biphenyl



To a mixture of 4-fluoro bromobenzene (1 g, 5.71 mmol) in 40 mL of dimethoxy ethane and Tetrakis palladium(0)($Pd(PPh_3)_4$), (56 mg, 0.03 mmol) was added aqueous Na_2CO_3 solution (3.6 g in 16 mL of water) and stirred at room temperature for 15 min and then was added 4-acetyl boronic acid (1.4 g, 8.56 mmol) and refluxed for 18 h. The reaction mixture was acidified with 1 N HCl and extracted with EtOAc. The organic layer was washed with water and then with brine, dried over Na_2SO_4, evaporated and purified the crude product over silica gel column by eluting with 15 % EtOAc+ Pet. ether to give 4-acetyl-4'-fluoro biphenyl as a creamish solid (0.98 g, 75 %).

^1H NMR (δ, $CDCl_3$, 200MHz): 8.20-7.40 (m, 4H), 7.13 (d, J=8.60Hz, 2H), 6.89 (d, J=8.60Hz, 2H), 2.64 (s, 3H).

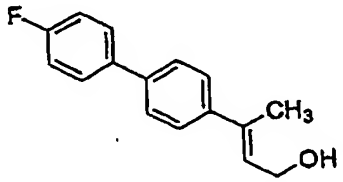
Step (ii): Preparation of 3-(4'-fluoro-biphenyl-4-yl)but-2-enoic acid ethyl ester



To the NaH (0.476 g, 5.91 mmol) in dry THF (5 mL) was added triethylphosphonoacetate (1.2 mL, 5.91 m mol) in 10 mL at 0 °C and stirred at room temperature for 30 min and then was added 4-acetyl-4'-fluoro biphenyl (0.9 g, 3.94 mmol), obtained in step (i), in 10 mL of THF at room temperature and the mixture was stirred at room temperature for 16 h and quenched with ice-water neutralized with 1N HCl and extracted with EtOAc and washed with water, dried and evaporated to give a crude compound which was purified over silica gel column to give a creamish solid of 3-(4'-fluoro-biphenyl-4-yl)but-2-enoic acid ethyl ester as a E-isomer (0.44 g, 48%).

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.70-7.50 (m, 4H), 7.26 (d, J=8.59 Hz, 2H), 7.12 (d, J=8.59 Hz, 2H), 6.20 (s, 1H), 4.23 (q, J=6.99 Hz, 2H), 2.61 (s, 3H), 1.33 (t, J=6.99 Hz, 3H).

Step (iii): Preparation of 3-(4'-fluoro-biphenyl-4-yl)but-2-ene-1-ol



The 3-(4'-fluoro-biphenyl-4-yl)but-2-enoic acid ethyl ester (0.44 g, 1.54 mmol), obtained in step (ii), was reduced with AlH_3 (prepared from LAH (0.176g) and $AlCl_3$ (0.206 g) in dry THF (10 mL) at −5 °C for 30 min. The reaction mixture was quenched with sat.Na_2SO_4 solution and filtered, washed with EtOAc and combined filtrates were evaporated to give 3-(4'-fluoro-biphenyl-4-yl)but-2-ene-1-ol as a white low melting solid (Yield:0.35g, 95%).

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.65 (m, 4H), 7.23 (d, J=8.59 Hz, 2H), 7.11 (d, J=8.59 Hz, 2H), 6.06 (t, J=6.98 Hz, 1H), 4.41 (d, J=6.98 Hz, 2H), 2.13 (s, 3H).

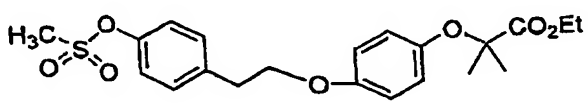
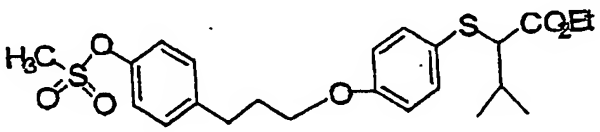
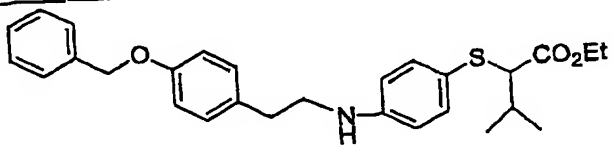
Step (iv): Preparation of ethyl-2-[4-[3-(4'-fluoro-biphenyl-4-yl)-but-2-enyloxy]phenoxyl-2-methylpropanoate

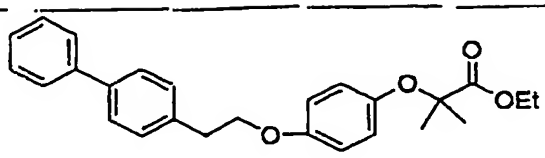
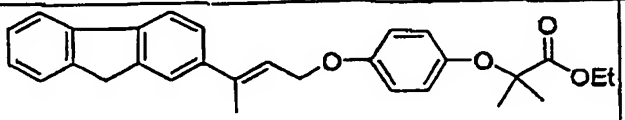
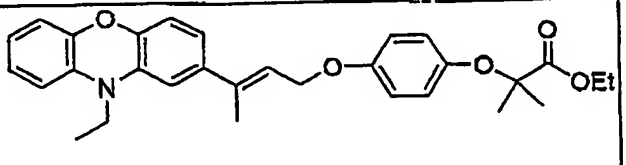
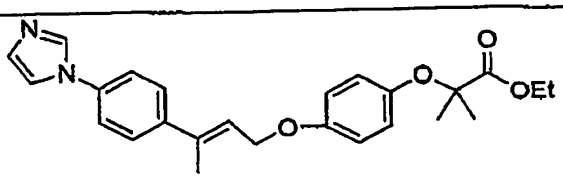
The 3-(4'-fluoro-biphenyl-4-yl)but-2-ene-1-ol (0.350 g), obtained in step (iii), was coupled with the ethyl-4-hydroxy phenoxy-2-methyl-propanoate (Ref: JMC, 2001, 44, 2061) (0.323 g) by Mitsinobu reaction using DIAD (0.436 g) and PPh_3 (0.572 g) in THF (10 mL) at 25 °C for 48 h. The reaction was worked up by diluting with more of EtOAc and washing with aqueous $KHSO_4$ solution and then with water, the dried solvent was evaporated and purified by column chromatography by eluting with 10% EtOAc and Pet. ether, to give 27% (0.17 g) of the ethyl-2-[4-[3-(4'-fluoro-biphenyl-4-yl)-but-2-enyl]phenoxy]-2-methyl-propanoate as an thick oil.

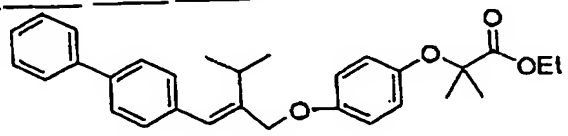
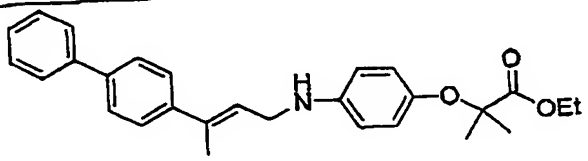
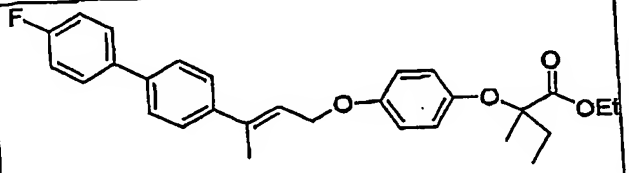
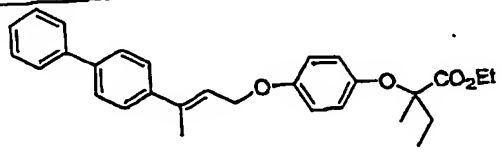
^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.50 (m, 8H), 7.14 (d, J=8.59 Hz, 2H), 6.84 (d, J=8.59 Hz, 2H), 6.10 (t, J=6.45 Hz, 1H), 4.71 (d, J=6.45 Hz, 2H), 4.24 (q, J=7.25 Hz, 2H), 2.15 (s, 3H), 1.56 (s, 6H), 1.28 (t, J=7.25 Hz, 3H).

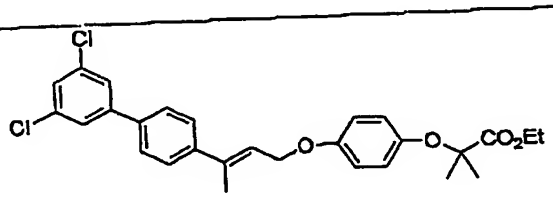
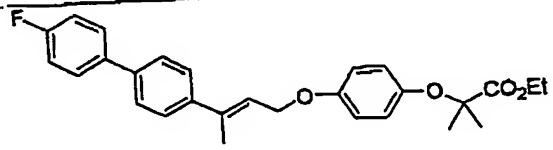
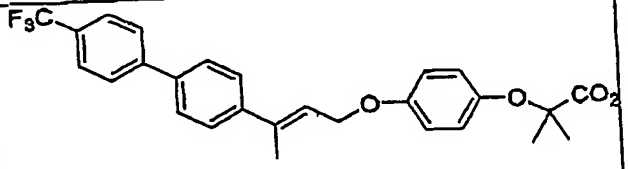
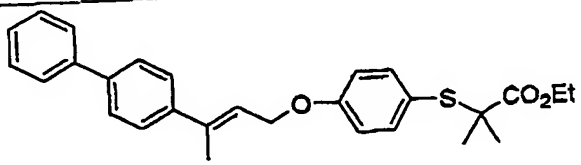
The following compounds falling into the general formula (I) have also been prepared by the process as defined in examples 1 and 2.

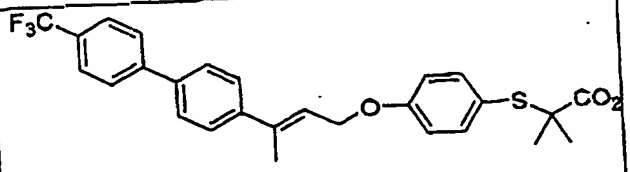
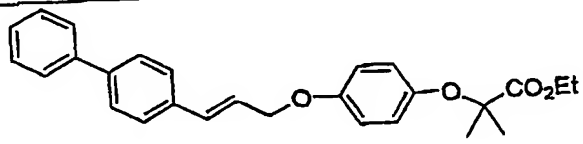
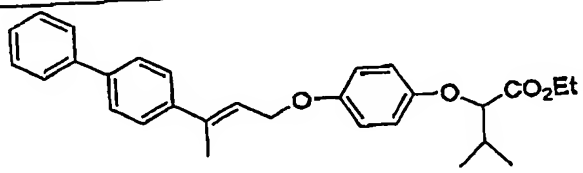
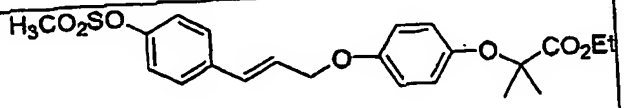
Example	Structure	Analytical Data

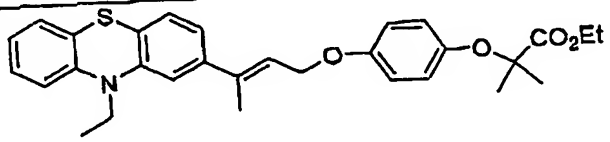
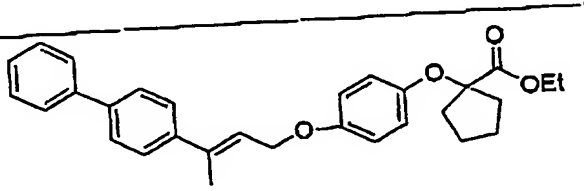
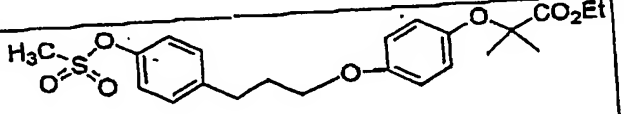
No.		
3		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.34-7.23(m, 4H), 6.85-6.72(m, 4H), 4.22(q, J=7.03Hz, 2H), 4.10(t, J=6.70Hz, 2H), 3.12(s, 3H), 3.07(t, J=6.70Hz, 2H), 1.52(s, 6H), 1.27(t, J=7.03Hz, 3H). Nature: Liquid.
4		^{1}H NMR (δ, CD_3OD, 200MHz): 7.40(d, J=8.59Hz, 2H), 7.30-7.15(m, 4H), 6.81(d, J=8.59Hz, 2H), 4.10(q, J=6.99 Hz, 2H), 3.94(t, J=5.91Hz, 2H), 3.25(d, J=9.13Hz, 1H), 3.13(s, 3H), 2.82(t, J=8.06Hz, 2H), 2.10-1.95(m, 3H), 1.25(t, J=6.99Hz, 3H), 1.17(d, 6.35Hz, 3H), 1.03(d, J=6.35Hz, 3H). Nature: Liquid.
5		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.42-7.20(m, 7H), 7.11(d, J=8.30Hz, 2H), 6.92(d, J= 8.30Hz, 2H), 6.65(d, J=8.30Hz, 2H), 5.05(s, 2H), 4.09(q, J=7.33Hz, 2H),3.35(t, J= 6.84Hz, 2H), 3.21(d, J=9.28Hz, 1H), 2.88(t, J=6.84Hz, 2H), 2.20-2.00(m, 1H), 1.22(t, J=7.33Hz, 3H), 1.14(d, J=6.83Hz, 3H) 1.02(d, J=6.83Hz, 3H). Nature: Liquid

6		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.12 (m, 9H), 6.80-6.86 (m, 4H), 4.12-4.29(m, 4H), 3.11(t, J=6.80Hz, 2H), 1.53(s, 6H), 1.27(t, J=7.0Hz, 3H). Nature:liquid
7		^{1}H NMR (δ, $CDCl_3$, 200MHz):7.80-7.20(m, 7H), 6.94(d, J=9.67Hz, 2H), 6.88(d, J=9.67Hz, 2H), 6.11(t, J=6.18Hz, 1H), 4.74(d, J=6.18Hz, 2H), 3.90(s, 2H), 2.20(s, 3H), 1.54(s, 6H). M.P: 155-158^{0}C.
8		^{1}H NMR (δ, $CDCl_3$, 200MHz): 6.92-6.60(m, 11H), 5.96(m, 1H), 4,67(d, J=6.10Hz, 2H), 4.15(q, J=7.10Hz, 2H), 3.71-3.68(m, 2H), 2.03(s, 3H), 1.45(s, 6H), 1.28-1.10(m, 6H). Nature: Liquid
9		^{1}H NMR (δ, $CDCl_3$, 200MHz): 8.40(s, 1H), 7.61(d, J=6.83Hz, 2H), 7.60-7.39(m, 4H), 6.88(d, J=9.27Hz, 2H), 6.85(d, J=9.27Hz, 2H), 6.13(t, J=4.88Hz, 1H), 4.73(d, J=4.88Hz, 2H), 4.27(q, J=7.31Hz, 2H), 2.19(s, 3H), 1.58(s, 6H), 1.32(t, J=7.31Hz, 3H).

10		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20(m, 9H), 6.83(d, J=9.14Hz, 2H), 6.78(d, J=9.14Hz, 2H), 6.64(s, 1H), 4.57(s, 2H), 4.23(q, J=7.25Hz, 2H), 2.80-2.60(m, 1H), 1.56(s, 6H), 1.54(d, J=6.34Hz, 3H), 1.22(t, J=7.25Hz, 3H), 1.19(d, J=6.34Hz, 3H). **Nature: Viscous liquid.**
11		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.61-7.30(m, 9H), 6.80(d, J=8.50Hz, 2H), 6.55(d, J=8.50Hz, 2H), 6.00-5.97(m, 1H), 4.23(q, J=7.00Hz, 2H), 3.90(d, J=6.40Hz, 2H), 2.15(s, 3H), 1.52(s, 6H), 1.28(t, J=7.00Hz, 3H). Nature: liquid.
12		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.44-7.20(M, 8H), 6.93(d, J=2.44Hz, 2H), 6.92(d, J=2.44 Hz, 2H), 6.04(t, J=6.45Hz, 1H), 4.69(d, J=6.45Hz, 2H), 4.25(q, J=6.98Hz, 2H), 2.14 (s, 3H), 1.95(q, J=7.52Hz, 2H), 1.43(s, 3H), 0.99(t, J=7.52 Hz, 3H), 0.88(t, J=6.98Hz, 3H). **Nature: liquid.**
13		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.63-7.30(m,9H); 6.85(d, J= 9.40Hz,2H);6.78(d, J=9.40Hz, 2H); 6.11(t, J=6.50Hz, 1H);

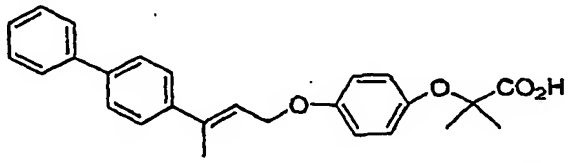
		4.71(d, J=6.50Hz,2H); 4.25(q, J=7.10Hz, 2H); 2.16(s, 3H); 1.95(q, J=7.52Hz,2H); 1.44 (s,3H); 1.29(t, J=7.10Hz, 3H); 0.99(t, J=7.52Hz, 3H). Nature: gummy liquid
14		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.25(m, 7H); 6.86(s, 4H); 6.13(t, J=5.86Hz, 1H); 4.72(d, J=5.86Hz, 2H); 4,25(q, J=7.32Hz, 2H); 2.16(s, 3H); 1.56(s,6H); 1.29(t, J=7.32Hz, 3H). Nature: Liquid.
15		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.00(m,8H); 6.91(d, J= 5.86Hz,2H);6.89(d, J=5.86Hz) ;6.09(t, J=6.18Hz,1H); 4.73 (d, J=6.18Hz, 2H); 2.17(s,3H) ;1.54(s, 6H).
16		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20(m, 8H); 6.90(d, J= 6.85Hz, 2H);6.88(d, J=6.85Hz, 2H); 6.11(t, J=6.11 Hz,1H); 4.76 (d, J=6.11Hz, 2H); 4.12(q, J=7.01Hz, 2H), 2.18(s,3H) ;1.46(s, 6H), 1.23(t, J=7.01Hz, 3H). Nature: Liquid.
17		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.63-7.33(m,11H); 6.91(d, J=8.30Hz,2H); 6.12 (t, J= 8.40Hz,1H); 4.77(d, J=6.40

		Hz,2H); 4.12(q, J=7.20Hz, 2H); 2.19(s,3H);1.40(s,6H); 1.23(t, J=7.20Hz, 3H). Nature: liquid.
18		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.78-7.50(m,8H); 7.40(d, J= 8.50Hz,2H); 6.92(d, J=8.50Hz, 2H) ; 6.11(t, J=6.15 Hz,1H); 4.76(d, J=6.15Hz, 2H); 4.12(q, J=7.0Hz, 2H); 2.18(s,3H); 1.46(s,6H); 1.23(t, J=7.0Hz, 3H).
19		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.70-7.20(m, 9H); 6.84 (s, 4H); 6.75(t, J=8.08Hz, 1H); 6.50-6.40(m, 1H); 4.66 (d, J=5.91Hz,2H); 4.24(q, J=7.25Hz, 2H); 1.54(s,6H); 1.26(t, J=7.52Hz, 3H). Nature: Liquid.
20		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.64-7.32(m,9H); 6.88 (s, 4H); 6.13(t, J=5.86Hz,1H); 4.72(d, J=5.86Hz,2H); 4.24(q, J=7.33Hz,2H); 2.40-2.20 (m, 1H), 2.18 (s, 3H); 1.27 (t, J=7.33Hz, 3H); 1.10 (d, J=4.88 Hz, 6H)
21		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.445(d, J=8.33Hz,2H); 7.23(d, J=8.33Hz,2H); 6.83(d, J=9.28 Hz,2H); 6.78(d, J=9.28Hz,2H), 6.69(d, J=16.12Hz,1H); 6.45-6.31(m, 1H); 4.65(d, J=5.37 Hz,

		2H); 4.22(q, J=7.25Hz, 2H), 3.14 (s,3H); 1.54(s,6H); 1.31-1.28(t, J=7.25Hz, 3H). Nature: Gummy solid.
22		^{1}H NMR (δ, DMSO-d^6, 200MHz): 7.20-6.76(m,11H); 6.01(t, J= 7.33Hz,1H); 4.67(d, J=5.60 Hz ,2H); 4.15 (q, J=7.0Hz, 2H), 3.96(q, J=6.72Hz, 2H) ;2.07(s,3H); 1.45 (s,6H); 1.33-1.15(m, 3H); 0.99(t, J=7.0Hz, 3H).
23		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.63-7.31(m, 9H), 6.89(d, J=9.28Hz, 2H), 6.78(d, J=9.28Hz, 2H), 6.11(t, J=5.86Hz, 1H), 4.71(d, J=5.86Hz, 2H), 4.22(q, J=7.33Hz, 2H), 2.40-2.00(m, 7H), 1.90-1.70(m, 4H), 1.21(t, J=7.33Hz, 3H). M.P. 112-114°C
24		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.26(d, J=6.17Hz, 2H), 7.20(d, J=6.17Hz, 2H), 6.83(d, J=6.72Hz, 2H), 6.75(d, J=6.72Hz, 2H), 4.24(q, J=6.98Hz,2H), 3.90(t, J=5.91Hz, 2H)3.13(s, 3H), 2.81(t,J=7.25Hz, 2H), 2.10-2.02 (m, 2H), 1.53(s, 6H), 1.28(t, J=6.98Hz, 3H).

Example 25:

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]-2-methyl propanoic acid

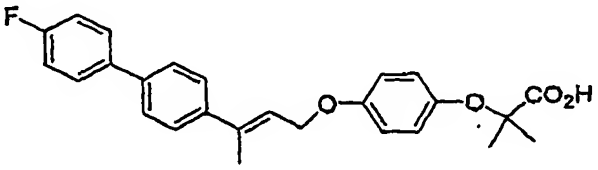


Ethyl-2-[4-(3-biphenyl-4-yl-but-2-enyl)-phenoxy]-2-methyl-propanoate (0.35 g), obtained in example 1, was hydrolysed with aqueous LiOH (0.35 g in 2 mL of water) at 25 °C for 12 h in methanol. THF mixture (3 mL+2 mL) after the completion of reaction the solvent was evaporated and the aqueous layer was washed once with ether and the aqueous layer was acidified with 2 N HCl to pH 2 and extracted with EtOAc and the organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give the title compound as a white solid in 90 % yield. Mp. 148-150 °C.

^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.25 (m, 9H), 6.88 (s, 4H), 6.08 (t, J=6.35 Hz, 1H), 4.72 (d, J=6.35 Hz, 2H), 2.15 (s, 3H), 1.49 (s, 6H).

Example 26:

2-[4-(3-(4'-Fluoro-biphenyl-4-yl-but-2-enyloxy)-phenoxy]-2-methyl-propanoic acid.

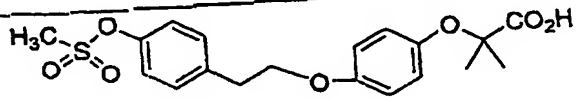
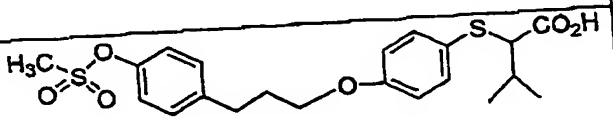
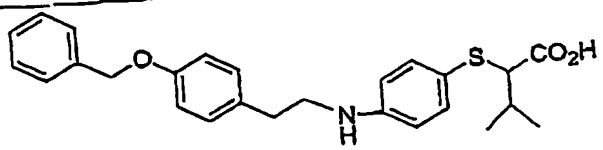
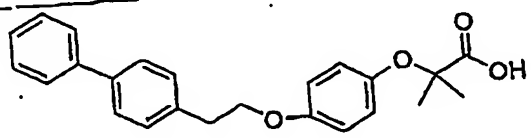


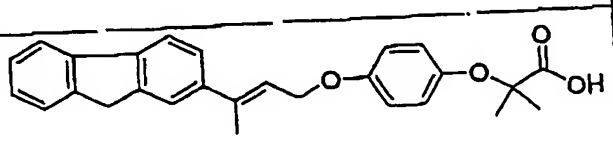
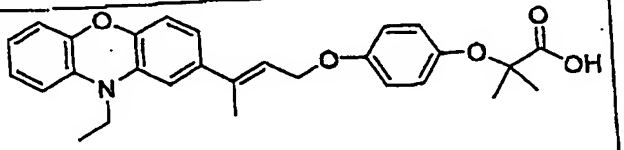
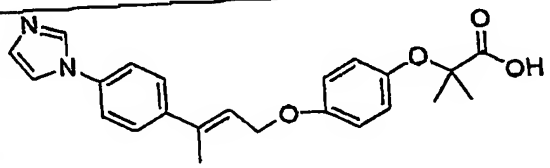
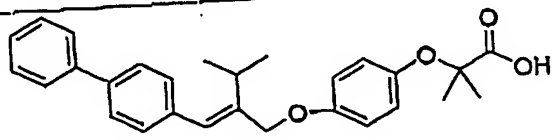
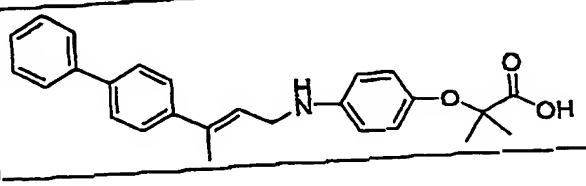
Ethyl-2-[4-[3-(4'-fluoro-biphenyl-4-yl)-but-2-enyl]phenoxy]-2-methylpropanoate (0.17 g), obtained in example 2, was hydrolysed with aqueous LiOH (0.79 g in 1 mL of water) at 25 °C for 12 h. in methanol:THF mixture (3 mL+2 mL). After completion of the reaction the solvent was evaporated and the aqeous layer was washed once with ether and the aqueous layer was acidified with 2 N HCl to pH 2 and extracted with EtOAc and the organic layer was dried with Na_2SO_4 and evaporated under reduced pressure to give the title compound as a white solid (Yield: 59%, 0.10 g). Mp.148-150 °C.

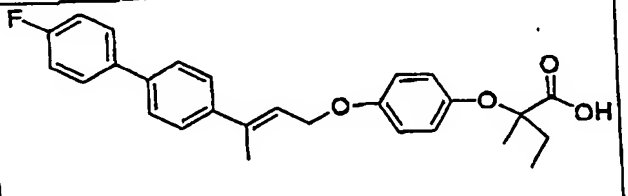
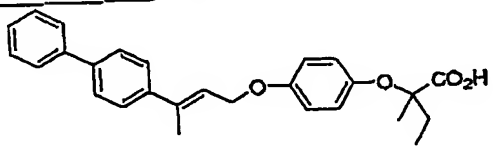
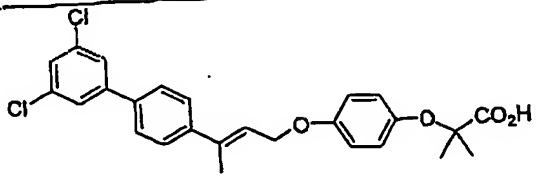
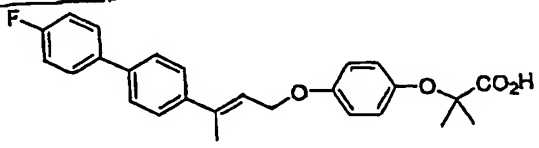
^{1}H NMR (200MHz): δ 7.60-7.00 (m, 8H), 6.91 (d, J= 5.86 Hz, 2H), 6.89 (d, J=5.86 Hz, 2H), 6.09 (t, J=6.18 Hz, 1H), 4.73 (d, J=6.18 Hz, 2H), 2.17 (s, 3H), 1.54 (s, 6H).

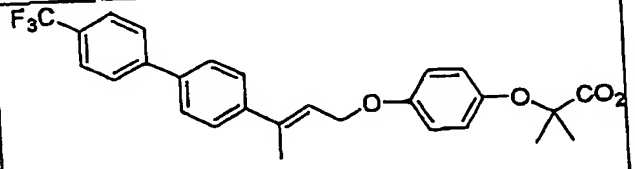
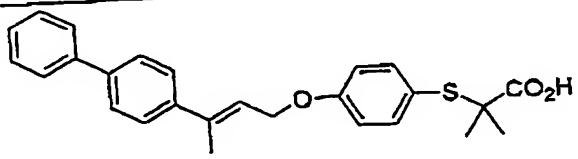
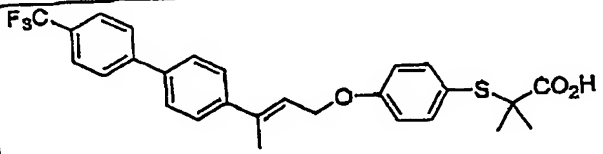
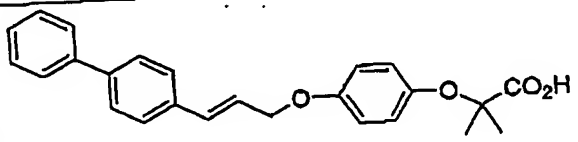
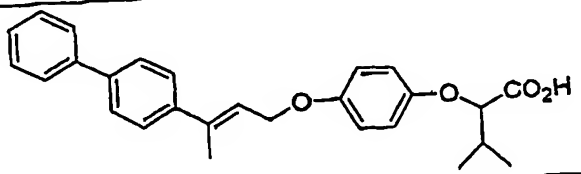
The following compounds falling into the general formula (I) have also been prepared by the process as defined in examples 26 and 27.

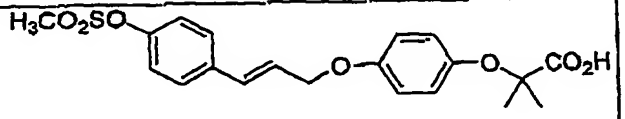
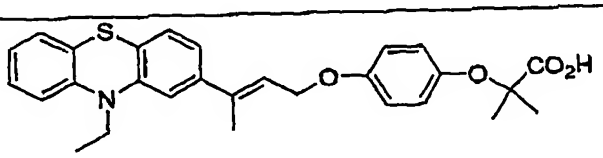
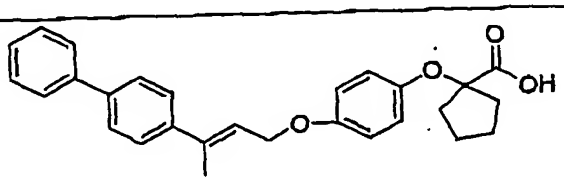
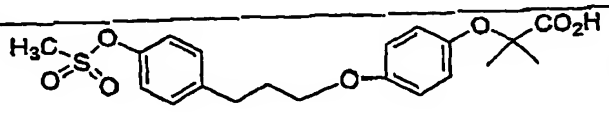
Example	Structure	Analytical Data

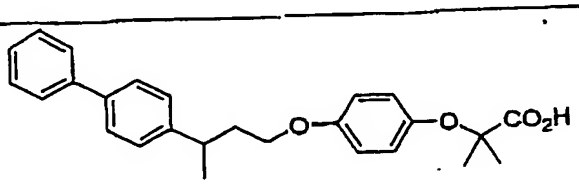
No.		
27		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.35-7.25(m, 4H), 6.90(d, J= 9.10Hz, 2H), 6.79(d, J=9.10Hz, 2H), 4.13(t, J=6.7Hz, 2H), 3.14(s, 3H), 3.07(t, J=6.7Hz, 2H), 1.53(s, 6H). Nature: Liquid.
28		^{1}H NMR (δ, CD_3OD, 200MHz): 7.41(d, J=8.79Hz, 2H), 7.02(d, J=8.30Hz, 2H), 6.86(d, J=8.79Hz, 2H), 6.69(d, J= 8.30Hz, 2H), 3.94(t, J=6.34Hz, 2H), 3.32(s, 3H), 3.22(d, J=9.28Hz, 1H), 2.70(t, J=8.31Hz, 2H), 2.10-1.95(m, 3H), 1.16(d, 6.35Hz, 3H), 1.04(d, J=6.35Hz, 3H). M.P: 115-118^{0}C
29		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.43-7.10(m, 9H), 6.90(d, J= 8.60Hz, 2H), 6.52(d, J=8.60Hz, 2H), 5.04(s, 2H), 3.25(t, J= 7.5Hz, 2H), 3.11(d, J=8.8Hz, 1H), 2.78(t, J=7.5Hz, 2H), 2.0-1.90(m, 1H), 1.08(d, J=6.7Hz, 3H), 1.02(d, J=6.7Hz, 3H). Nature: Liquid
30		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.66-7.58 (m, 4H), 7.48-7.34 (m, 5H), 6.83-6.77(m, 4H), 4.15(t, J=6.6Hz, 2H), 3.02(t, J= 6.6Hz, 2H), 1.42(s, 6H).

		M.P:138-140^{0}C.
31		^{1}H NMR (δ, $CDCl_3$, 200MHz):7.80-7.20(m, 7H), 6.94(d, J=9.67Hz, 2H), 6.88(d, J=9.67Hz, 2H), 6.11(t, J=6.18Hz, 1H), 4.74(d, J=6.18Hz, 2H), 3.90(s, 2H), 2.20(s, 3H), 1.54(s, 6H). M.P: 155-158^{0}C.
32		^{1}H NMR (δ, $CDCl_3$, 200MHz): 6.81(m, 11H), 5.95(m, 1H), 4,62(d, J=5.8Hz, 2H), 3.69(q, J=6.30Hz, 2H), 2.02(s, 3H), 1.35(s, 6H), 1.12(t, J=6.30Hz, 3H). M.P: 114-116^{0}C
33		^{1}H NMR (δ, DMSO-d^6, 200MHz): 8.24(s, 1H), 7.73(bs, 1H), 7.60(d, J=6.83Hz, 2H), 7.57(d, J=6.83Hz, 2H), 7.09(bs, 1H), 6.88(d, J=8.77Hz, 2H), 6.08(t, J=5.85Hz, 1H), 4.70(d, 5.85 Hz, 2H), 2.11(s, 3H), 1.43(s, 6H).
34		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.20(m, 9H), 6.65(s, 1H), 4.60(s, 2H), 2.80-2.60(m, 1H), 1.53(s, 6H), 1.24(d, J=6.34Hz, 3H), 1.19(d, J=6.34Hz, 3H). **Nature: Viscous liquid.**
35		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.65-7.53(m, 3H), 7.49-7.35(m, 6H), 6.71(d, J=8.60Hz, 2H),

		6.50(d, J=8.60Hz, 2H), 5.96(m,1H), 3.81(d, J=5.90Hz, 2H), 2.11(s, 3H), 1.37(s, 6H) M.P:184-188°C
36		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.44-7.20(M, 8H), 6.93(d, J=2.44Hz, 2H), 6.92(d, J=2.44 Hz, 2H), 6.02(t, J=6.35Hz, 1H), 4.71(d, J=6.35Hz, 2H), 2.14(s, 3H), 2.0-1.80(m, 2H), 1.42(s, 3H), 1.06(t, J=7.32Hz, 3H). **M.p: 122-125°C.**
37		^{1}H NMR (200MHz): δ 7.70-7.30 (m, 9H), 6.96 (d, J= 9.40 Hz, 2H), 6.89 (d, J=9.40 Hz, 2H), 6.12 (t, J=6.18 Hz, 1H), 4.75 (d, J=6.18 Hz, 2H), 2.19 (s, 3H), 1.97 (q, J=7.52 Hz, 2H), 1.45 (s, 3H), 1.08 (t, J=7.52 Hz, 3H). Mp: 114-117 °C
38		^{1}H NMR (200MHz): δ 7.60-7.25 (m, 7H), 6.93 (d, J= 5.37Hz, 2H), 6.87 (d, J=5.37 Hz, 2H), 6.13 (t, J=5.86 Hz, 1H), 4.75 (d, J=5.86 Hz, 2H), 2.18 (s, 3H), 1.57 (s, 6H). Mp: 52-54 °C
39		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.60-7.40(m, 6H), 7.30-7.00(m, 2H), 6.91(d, J=9.20Hz, 2H), 6.89(d, J=9.20Hz, 2H), 6.09(t, J=6.18Hz, 1H), 4.73(d, J=6.18Hz, 2H), 2.17(s, 3H),

		1.54(s, 6H). M.P. 148-150^{0}C
40		^{1}H NMR (200MHz): δ 7.60-7.20 (m, 8H), 6.91 (d, J= 6.86 Hz, 2H), 6.89 (d, J=6.86 Hz, 2H), 6.09 (t, J=6.48 Hz, 1H), 4.73 (d, J=6.48 Hz, 2H), 2.12 (s, 3H), 1.49 (s, 6H). Mp: 150-154 °C
41		^{1}H NMR (200MHz): δ 7.70-7.25 (m, 11H), 6.92 (d, J=8.59 Hz, 2H), 6.10 (t, J= 6.17 Hz, 1H), 4.76 (d, J=6.17 Hz, 2H), 2.16 (s, 3H),1.49 (s, 6H) Mp: 162-165 °C
42		^{1}H NMR (200MHz): δ 7.78-7.50 (m, 8H), 7.46 (d, J= 8.86 Hz, 2H), 6.92 (d, J=8.86 Hz, 2H), 6.11(t, J=6.45 Hz, 1H), 4.77 (d, J=6.45 Hz, 2H), 2.17 (s, 3H), 1.49 (s, 6H). Mp: 142-146 °C
43		^{1}H NMR (200MHz): δ 7.80-7.25 (m, 9H), 6.92 (d, J= 8.86 Hz, 2H), 6.82 (d, J=8.86 Hz, 2H), 6.64 (d, J=9.27 Hz, 1H), 6.62-6.40 (m, 1H), 4.68 (d, J=5.37 Hz, 2H), 1.44 (s, 6H) Mp: 172-174 °C
44		^{1}H NMR (200MHz): δ 7.80-7.30 (m, 9H), 6.92 (d, J= 9.13 Hz, 2H), 6.82 (d, J=9.13 Hz, 2H), 6.09 (t, J=6.18 Hz, 1H), 4.72 (d,

		J=6.18 Hz, 2H), 4.34 (d, J=5.11 Hz, 1H), 2.30-2.00 (m, 4H), 1.02 (d, J=5.72 Hz, 3H), 0.99 (d, J=5.72 Hz, 3H). Mp: 136-140 °C
45		^{1}H NMR (200MHz): δ 7.45 (d, J=8.79 Hz, 2H), 7.25 (d, J=8.79 Hz, 2H), 6.92 (d, J=9.28 Hz, 2H), 6.84 (d, J=9.28 Hz, 2H), 6.71 (d, J=16.11 Hz, 1H), 6.50-6.30 (m, 1H), 4.65 (d, J=5.37 Hz, 2H), 3.15 (s, 3H), 1.54 (s, 6H) Mp: 112-114 °C
46		^{1}H NMR (200MHz): δ 7.20-6.78 (m, 11H), 6.01 (t, J= 7.33 Hz, 1H), 4.67 (d, J=7.33 Hz. , 2H), 3.95 (q, J=6.82 Hz, 2H), 2.06 (s, 3H), 1.43 (s, 6H), 1.29 (t, J=6.82 Hz, 3H).
47		^{1}H NMR (200MHz): δ 7.70-7.30 (m, 9H), 6.87 (d, J=9.28 Hz, 2H), 6.79 (d, J+9.28 Hz, 2H), 6.10 (t, J=5.86 Hz, 1H), 4.71 (d, J=5.8Hz, 2H), 2.35-2.18 (m, 4H), 2.16 (s, 3H), 1.90-1.70 (m, 4H) Mp: 142-144 °C
48		^{1}H NMR (δ, $CDCl_3$, 200MHz): 7.34 (d, J=8.30Hz, 2H), 7.26 (d, J=8.30Hz, 2H), 6.82 (s, 4H), 3.91 (t, J=6.35Hz, 2H), 2.75 (t, J=7.33Hz, 2H), 2.03-1.90 (m,

		2H), 1.43 (s, 6H). M.P: 64 - 66°C
49		^{1}H NMR (200MHz): δ 7.65-7.20(m, 9H), 6.85 (d, J=8.79 Hz, 2H), 6.74 (d, J=8.79 Hz, 2H), 3.90-3.75 (m, 2H), 3.20-3.0 (m, 1H), 2.20-2.00 (m, 2H), 1.47 (s, 6H), 3.33 (d, J=6.86 Hz, 3H). Mp: 120-122 °C

The compounds of the present invention lower triglyceride, total cholesterol, LDL, VLDL, random blood sugar level and increase HDL by agonistic mechanism. This may be demonstrated by *in vitro* as well as *in vivo* animal experiments

(A) *In vitro*:

(a) Determination of hPPARα activity:

Ligand binding domain of hPPARα was fused to DNA binding domain of Yeast transcription factor Gal 4 in eucaryotic expression vector. Using superfect (Qiagen, Germany) as transfecting reagent HEK-293 cells are transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound can be added at different concentrations after 42 hrs of transfection and incubated overnight. Luciferase activity as a function of compound binding/activation capacity of PPARα will be measured using Packard Luclite kit (Packard, USA) in Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141; Superfect Transfection Reagent Handbook. February 1997. Qiagen, Germany).

(b) Determination of hPPARγ activity

Ligand binding domain of hPPARγ1 is fused to DNA binding domain of Yeast transcription factor GAL4 in eucaryotic expression vector. Using lipofectamine (Gibco BRL, USA) as transfecting reagent HEK-293 cells are transfected with this plasmid and a reporter plasmid harboring the luciferase gene driven by a GAL4 specific promoter. Compound can be added at 1 μM concentration after 48 hrs of transfection and incubated overnight. Luciferase activity as a function of drug binding/activation capacity of PPARγ1 will be measured using Packard Luclite kit (Packard, USA) in Packard Top Count (Ivan Sadowski, Brendan Bell, Peter Broag and Melvyn Hollis. Gene. 1992. 118 : 137 –141;

Guide to Eukaryotic Transfections with Cationic Lipid Reagents. Life Technologies, GIBCO BRL, USA).

Example No	Concentration(μM)	PPARα	Concentration(μM)	PPARγ
Example 37	50	12.2	1	2.8
Example 40	50	12.6	1	1.3

(c) Determination of HMG CoA reductase inhibition activity

Liver microsome bound reductase is prepared from 2% cholestyramine fed rats at mid-dark cycle. Spectrophotometric assays are carried out in 100 mM KH_2PO_4, 4 mM DTT, 0.2 mM NADPH, 0.3 mM HMG CoA and 125 μg of liver microsomal enzyme. Total reaction mixture volume was kept as 1 ml. Reaction was started by addition of HMG CoA. Reaction mixture is incubated at 37 °C for 30 min and decrease in absorbance at 340 nm was recorded. Reaction mixture without substrate was used as blank (Goldstein, J. L and Brown, M. S. Progress in understanding the LDL receptor and HMG CoA reductase, two membrane proteins that regulate the plasma cholesterol. J. Lipid Res. 1984, 25: 1450 – 1461). The test compounds will inhibited the HMG CoA reductase enzyme.

(B) *In vivo*

(a) Efficacy in genetic models

Mutation in colonies of laboratory animals and different sensitivities to dietary regimens have made the development of animal models with non-insulin dependent diabetes and hyperlipidemia associated with obesity and insulin resistance possible. Genetic models such as db/db and ob/ob (Diabetes, (1982) 31(1) : 1- 6) mice and zucker fa/fa rats have been developed by the various laboratories for understanding the pathophysiology of disease and testing the efficacy of new antidiabetic compounds (Diabetes, (1983) 32: 830-838; Annu. Rep. Sankyo Res. Lab. (1994). 46 : 1-57). The homozygous animals, C57 BL/KsJ-db/db mice developed by Jackson Laboratory, US, are obese, hyperglycemic, hyperinsulinemic and insulin resistant (J. Clin. Invest., (1990) 85 : 962-967), whereas heterozygous are lean and normoglycemic. In db/db model, mouse progressively develops insulinopenia with age, a feature commonly observed in late stages of human type II diabetes when blood sugar levels are insufficiently controlled. The state of pancreas and its course vary according to the models. Since this model resembles that

of type II diabetes mellitus, the compounds of the present invention will be tested for blood sugar and triglycerides lowering activities.

Male C57BL/KsJ-db/db mice of 8 to 14 weeks age, having body weight range of 35 to 60 grams, bred at Dr. Reddy's Research Foundation (DRF) animal house, were used in the experiment. The mice are provided with standard feed (National Institute of Nutrition (NIN), Hyderabad, India) and acidified water, ad libitum. The animals having more than 350 mg / dl blood sugar will be used for testing. The number of animals in each group will be 4.

Test compounds are suspended on 0.25% carboxymethyl cellulose and administered to test group at a dose of 0.1 mg to 30 mg / kg through oral gavage daily for 6 days. The control group receives vehicle (dose 10 ml / kg). On 6th day the blood samples will be collected one hour after administration of test compounds / vehicle for assessing the biological activity.

The random blood sugar and triglyceride levels can be measured by collecting blood (100 µl) through orbital sinus, using heparinised capillary in tubes containing EDTA which was centrifuged to obtain plasma. The plasma glucose and triglyceride levels can be measured spectrometrically, by glucose oxidase and glycerol-3-PO_4 oxidase/peroxidase enzyme (Dr. Reddy's Lab. Diagnostic Division Kits, Hyderabad, India) methods respectively.

The blood sugar and triglycerides lowering activities of the test compound are calculated according to the formula.

Compound	Dose (mg / kg)	Triglyceride Lowering (%)
Example 37	1	52

(b) Plasma triglyceride and Cholesterol lowering activity in hypercholesterolemic rat models

Male Sprague Dawley rats (NIN stock) were bred in DRF animal house. Animals were maintained under 12 hour light and dark cycle at 25 ± 1 °C. Rats of 180 - 200 gram body weight range were used for the experiment. Animals are made hypercholesterolemic by feeding 2% cholesterol and 1% sodium cholate mixed with standard laboratory chow [National Institute of Nutrition (NIN), Hyderabad, India] for 6 days. Throughout the experimental period the animals were maintained on the same diet (Petit, D., Bonnefis, M.

T., Rey, C and Infante, R. Effects of ciprofibrate on liver lipids and lipoprotein synthesis in normo- and hyperlipidemic rats. Atherosclerosis. 1988. 74 : 215 – 225).

The test compounds can be administered orally at a dose 0.1 to 30 mg/kg/day for 3 days. Control group was treated with vehicle alone (0.25% Carboxymethylcellulose; dose 10 ml/kg).

The blood samples can be collected in fed state 1 hour after drug administration on 0 and 3 day of compound treatment. The blood can be collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample will be separated for total cholesterol, HDL and triglyceride estimations. Measurement of plasma triglyceride, total cholesterol and HDL are were done using commercial kits (Dr. Reddy's Laboratory, Diagnostic Division, India). LDL and VLDL cholesterol can be calculated from the data obtained for total cholesterol, HDL and triglyceride. The reduction of various parameters examined are calculated according to the formula.

Compound	Dose (mg / kg)	Reduction in Total Cholesterol (%)	Triglyceride Lowering (%)	Increase in High Density Lipoprotien (%)	Reduction in Low Density Lipoprotien (%)
Example 37	1	60	55	70	64

(c) Plasma triglyceride and total cholesterol lowering activity in Swiss albino mice

Male Swiss albino mice (SAM) were obtained from NIN and housed in DRF animal house. All these animals are maintained under 12 hour light and dark cycle at 25 ± 1 ^{0}C. Animals are given standard laboratory chow (NIN, Hyderabad, India) and water, *ad libitum*. SAM of 20 - 25 g body weight range and Guinea pigs of 500 - 700 g body weight range are used (Oliver, P., Plancke, M. O., Marzin, D., Clavey, V., Sauzieres, J and Fruchart, J. C. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. Atherosclerosis. 1988. 70 : 107 – 114).

The test compounds can be administered orally to Swiss albino mice at 0.3 to 30 mg/kg/day dose for 6 days. Control mice are treated with vehicle (0.25% Carboxymethylcellulose; dose 10 ml/kg). The test compounds are administered orally to Guinea pigs at 0.3 to 30 mg/kg/day dose for 6 days. Control animals are treated with vehicle (0.25% Carboxymethylcellulose; dose 5 ml/kg).

The blood samples can be collected in fed state 1 hour after drug administration on 0 and 6 day of treatment. The blood can be collected from the retro-orbital sinus through heparinised capillary in EDTA containing tubes. After centrifugation, plasma sample was separated for triglyceride (Wieland, O. Methods of Enzymatic analysis. Bergermeyer, H. O., Ed., 1963. 211 - 214; Trinder, P. Ann. Clin. Biochem. 1969. 6: 24 – 27). Measurement of plasma triglyceride is done using commercial kits (Dr. Reddy's Diagnostic Division, Hyderabad, India).

Compound	Dose (mg / kg)	Triglyceride Lowering (%)
Example 37	3	71

(d) Body weight reducing effect in cholesterol fed hamsters :

Male Syrian Hamsters are procured from NIN, Hyderabad, India. Animals are housed at DRF animal house under 12 hour light and dark cycle at 25 ± 1 ^{0}C with free access to food and water. Animals are maintained with 1% cholesterol containing standard laboratory chow (NIN) from the day of treatment.

The test compounds can be administered orally at 1 to 30 mg/kg/day dose for 15 days. Control group animals are treated with vehicle (Mill Q water, dose 10 ml/kg/day). Body weights are measured on every 3rd day.

Compound	Dose (mg / kg)	Reduction in Total Cholesterol (%)	Reduction in Triglyceride (%)	Reduction in Body weight (%)
Example 25	3	55	45	22

Formulae for calculation:

1. Percent reduction in Blood sugar / triglycerides / total cholesterol will be calculated according to the formula :

$$\text{Percent reduction (\%)} = \left[1 - \frac{TT/OT}{TC/OC}\right] \times 100$$

OC = Zero day control group value

OT = Zero day treated group value

TC = Test day control group value

TT = Test day treated group value

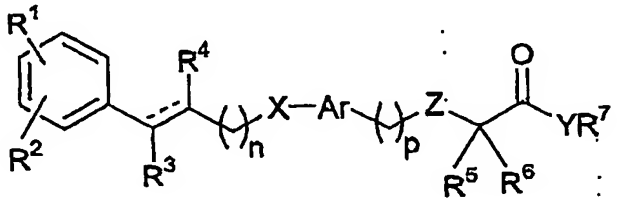
2. LDL and VLDL cholesterol levels will be calculated according to the formula:

LDL cholesterol in mg/dl = [Total cholesterol - HDL cholesterol - $\frac{\text{Triglyceride}}{5}$] mg/dl

VLDL cholesterol in mg/dl=[Total cholesterol-HDL cholesterol-LDL cholesterol] mg/dl.

We claim:

1. Novel compounds of the formula (I), pharmaceutically acceptable salts thereof as well as pharmaceutical compositions containing them wherein:



(I)

R^1 and R^2 are same or different and independently represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted group selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroarylcarbonyl, aryloxy, aralkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, heteroarylcarbonylamino, heteroaryl, heterocyclyl, heteroaralkoxy, heteroaryloxy, fluorenylmethoxycarbonyl (Fmoc), fluorenylmethoxycarbonylamino (N-Fmoc), -OSO_2R^8, -$OCONR^8R^9$, NR^8COOR^9, -NR^8COR^9, -NR^8R^9, -$NR^8SO_2R^9$, $NR^8CONR^9R^{10}$, -$NR^8CSNR^8R^9$, -SO_2R^8, -SOR^8, -SR^8, -$SO_2NR^8R^9$, -SO_2OR^8, $CONR^8R^9$, $COOR^9$, COR^9, wherein R^8, R^9 and R^{10} may be same or different and independently represent hydrogen, alkyl, aryl, aralkyl, aryloxy or heteroaryl or R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring, which may optionally contain up to 3 heteroatoms selected from N, S, or O and may be unsubstituted or have up to 4 substituents which may be identical or different.

R^3 and R^4 are same or different and independently represent represent hydrogen, halogen, optionally substituted alkyl, cycloalkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group.

'n' and 'p' represent 0-6.

X represents O, S, NR where R represents hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, alkanoyl, or aroyl.

'Ar' represents optionally substituted, divalent, single or fused aromatic, heteroaromatic or heterocyclic group.

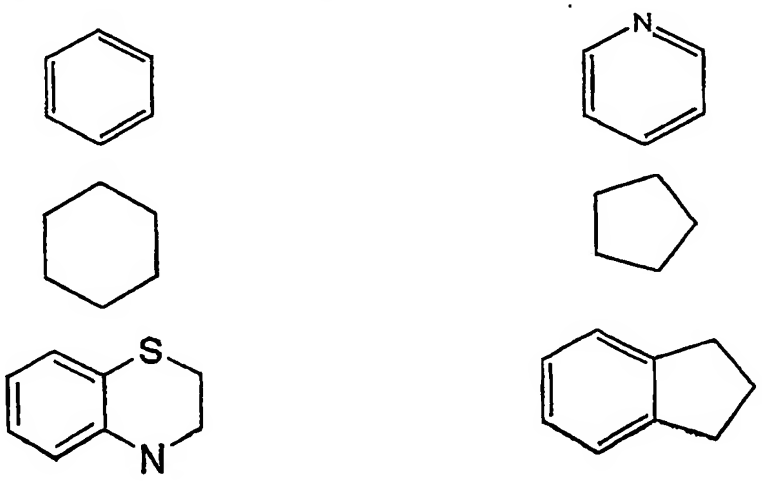
Z represents O, S, NR where R is as defined above.

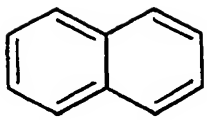
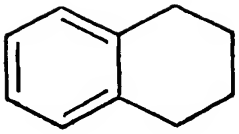
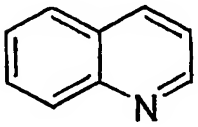
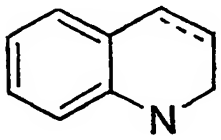
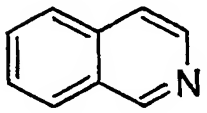
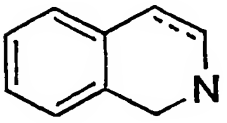
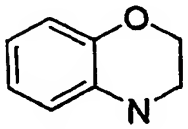
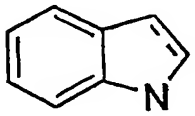
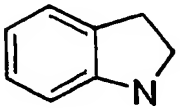
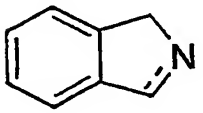
R^5 and R^6 are same or different and independently represent hydrogen, hydroxy, halogen or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, aryl, aralkyl or heteroaralkyl groups. R^5 and R^6 together may form a 5 or 6 membered cyclic rings, which may contain one or two hetcro atoms selected from O, S or N.

Y represents oxygen or NR^{11} where R^{11} represent hydrogen, optionally substituted groups selected from alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl or heteroaryl.
R^7 and R^{11} together may also form a 5 or 6 membered cyclic ring, which may contain one or two hetero atoms selected from O, S or N.
'----' represents a bond or no bond.

2. The compound of claim 1 wherein
R^1 and R^2 are same or different and independently represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted alkyl, alkoxy, aryl, aralkyl, aralkoxy, heteroaryl, heteroaralkoxy, $-OSO_2R^8$, $-SO_2R^8$, NR^8R^9;
R^3 and R^4 are same or different and independently represent hydrogen, halogen, optionally substituted alkyl, aralkyl;
R^5 and R^6 are same or different and independently represent hydrogen, hydroxy, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered aromatic or non aromatic cyclic ring system optionally containing 1 or 2 heteroatoms selected from O, S or N;
R^7 and R^{11} may for a cyclic ring system selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolinyl, diazolinyl and the like.

3. A compound of claim 1 wherein:
R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring selected from:



4. A compound of claim 2 wherein:

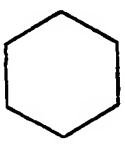
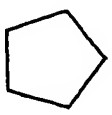
R^1 and R^2 are same or different and independently represent hydrogen, halogen, nitro, amino, hydroxy or optionally substituted alkyl, aryl, aralkyl, aralkoxy, heteroaryl, heteroaralkoxy, $-OSO_2R^8$;

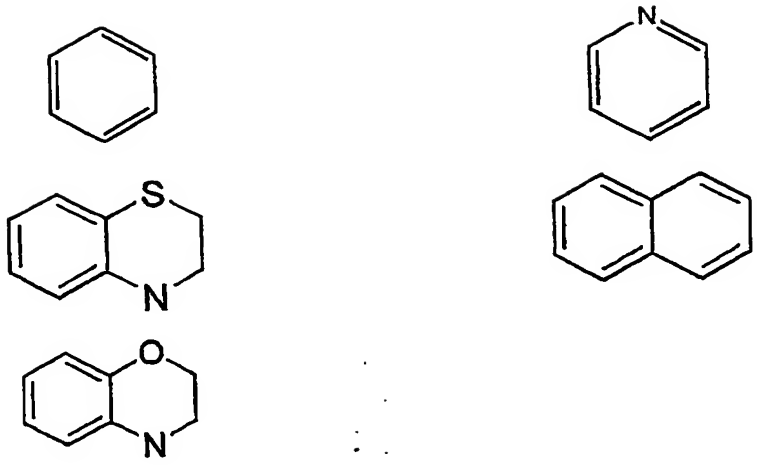
R^3 and R^4 are same or different and independently represent hydrogen, optionally substituted alkyl;

R^5 and R^6 are same or different and independently represent hydrogen, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered saturated cyclic ring system

5. A compound of claim 1 wherein:

R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring selected from:



R^3 and R^4 are same or different and independently represent hydrogen, optionally substituted alkyl;

R^5 and R^6 are same or different and independently represent hydrogen, optionally substituted alkyl, cycloalkyl, aryl or R^5 and R^6 together form a 5 or 6 membered saturated cyclic ring system;

6. A compound of claim 1 wherein

R^1 is selected from $-OSO_2CH_3$, halogen, alkyl optionally substituted phenyl wherein the substituent is selected from alkyl or halogen

R^2, R^3, R^4, R^5, R^6 and R^7 are same or different and independently represent hydrogen, methyl, ethyl or propyl

'Ar' represents optionally substituted phenyl wherein the substituent is C_{1-10}alkyl

X, Y and Z independently represent oxygen

n and p independently represent 0 or 1

7. R^1 is selected from optionally substituted phenyl wherein the substituent is selected from halogen

R^2, R^3, R^4, R^5, R^6 and R^7 are same or different and independently represent hydrogen, methyl, ethyl or propyl

'Ar' represents optionally substituted phenyl wherein the substituent is C_{1-10}alkyl

X, Y and Z independently represent oxygen

n and p independently represent 0 or 1

8. A compound of formula I selected from:

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(3-biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionioc

Ethyl 2-{4-[3-(4'-fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butyric acid

Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butanote

2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionic acid

Ethyl 2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionic acid

Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionate

2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionic acid

Ethyl 2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butyric acid

Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butanoate

2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionate

1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid
1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid ethyl ester.

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionate

2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionate

2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butyric acid
Ethyl 2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butanote

2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionate

2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butyric acid
Ethyl 2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butanote

9. A compound of formula I selected from:
2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl propionate

2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-ethoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-allyloxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-butoxy)phenoxy]2-methyl propionate

10. A compound of formula I selected from:
2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionioc
Ethyl 2-{4-[3-(4'-fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butyric acid
Ethyl 2-{4-[3-(4'-Fluoro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl butanote

2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(3',5'-dichloro biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionic acid
Ethyl 2-{4-[3-(4'-trifluoromethyl biphenyl-4-yl)but-2-enyloxy]phenylsulfanyl}2-methyl propionate

11. A compound of formula I selected from:
2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(2-Biphenyl-4-yl-methylene-3-methyl butoxy)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butyric acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]2-methyl butanote

2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butyric acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]3-methyl butanoate

1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid
1-[4-(3-Biphenyl-4-yl-but-2-enyloxy)phenoxy]cyclopentane carboxylic acid ethyl ester.

12. A compound of formula I selected from:
2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-yl-but-2-enylamino)phenoxy]2-methyl propionate

2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionic acid
Ethyl 2-[4-(3-Biphenyl-4-ylbut-2-enyloxy)phenylsulfanyl]2-methyl propionate

13. A compound of formula I selected from;

2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(4-Methanesulfonyloxy phenyl)ethoxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenylsulfanyl}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Methanesulfonyloxy phenyl)propoxy]phenoxy}2-methyl propionate

14. A compound of formula I selected from:
2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butyric acid
Ethyl 2-{4-[2-(4-Benzyloxy phenyl)ethylamino]phenylsulfanyl}3-methyl butanote

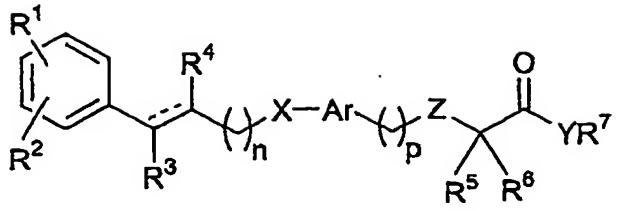
2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[2-(9H-Fluoren-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenoxazin-2-yl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(4-Imidazol-1-yl-phenyl)but-2-enyloxy]phenoxy}2-methyl propionate

2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionic acid
Ethyl 2-{4-[3-(10-Ethyl-10H-phenothiazin-2-yl)but2-enyloxy]phenoxy}2-methyl propionate

15. A process for the preparation of compound of formula (I)



(I)

wherein:

R^1 and R^2 are same or different and indcpendcntly represent hydrogen, halogen, nitro, cyano, amino, hydroxy or optionally substituted group selectcd from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, alkylcarbonyl, alkoxycarbonyl, arylcarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroarylcarbonyl, aryloxy, aralkoxy, alkylcarbonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, heteroarylcarbonylamino, heteroaryl, heterocyclyl, heteroaralkoxy, heteroaryloxy, fluorenylmethoxycarbonyl (Fmoc), fluorcnylmethoxycarbonylamino (N-Fmoc), -OSO_2R^8, -$OCONR^8R^9$, NR^8COOR^9, -NR^8COR^9, -NR^8R^9, -$NR^8SO_2R^9$, $NR^8CONR^9R^{10}$, -$NR^8CSNR^8R^9$, -SO_2R^8, -SOR^8, -SR^8, -$SO_2NR^8R^9$, -SO_2OR^8, $CONR^8R^9$, $COOR^9$, COR^9, wherein R^8, R^9 and R^{10} are same or different and indcpcndcntly represent hydrogen, alkyl, aryl, aralkyl, aryloxy or heteroaryl or R^1 and R^2 together form a monocyclic or polycyclic aromatic or non aromatic ring or an aromatic ring fused to a non aromatic ring, which may optionally contain up to 3 heteroatoms selected from N, S, or O and are unsubstituted or have up to 4 substituents which are identical or different.

R^3 and R^4 are samc or different and independcntly represent represent hydrogen, halogen, optionally substituted alkyl, cycloalkyl, alkanoyl, aryl, aroyl, aralkyl or aralkanoyl group.

'n' and 'p' reprcsent 0-6.

X represents O, S, NR where R represents hydrogen or optionally substituted groups selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, alkanoyl, or aroyl.

'Ar' represents optionally substituted, divalent, single or fused aromatic, hctcroaromatic or heterocyclic group.

Z represents O, S, NR where R is as defined above.

R^5 and R^6 are same or different and independently represent hydrogen, hydroxy, halogen or optionally substituted groups selected from alkyl, cycloalkyl, alkoxy, aryl, aralkyl or heteroaralkyl groups. R^5 and R^6 togcther may form a 5 or 6 membered cyclic rings, which may contain one or two hetero atoms selected from O, S or N.

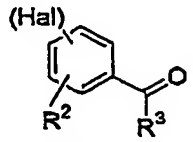
Y represents oxygen or NR^{11} where R^{11} represent hydrogen, optionally substituted groups selected from alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclyl or heteroaryl.

R^7 and R^{11} together may also form a 5 or 6 membered cyclic ring, which may contain one or two hetero atoms selected from O, S or N.

'----' represents a bond or no bond.

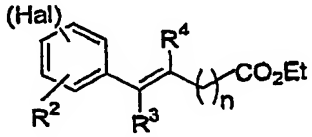
which comprises:

a) i. Reacting the compound of formula (Ia)



(Ia)

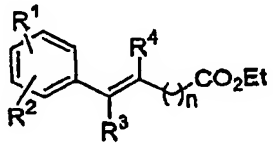
where 'Hal' represents a halogen atom selected bromine or iodine, R^2 is hydrogen and R^3 is as defined, in a Witting-Horner reaction manner, by using phosphono acetate compounds selected from triethyl phosphono acetates, trimethylphosphono acetate or Ph_3P^+-CH_2^--CO_2Et in the presence of a base selected from sodium hydride, potassium tertiary butoxide, potassium hydroxide, sodium methoxide or sodium ethoxide. The solvent used in the reaction is selected from alcohol selected from methanol, ethanol, propanol, isopropanol or tetrahydrofuran, ether, dioxane, dimethoxyethane or a mixture thereof at a temperature range of 0 to 10 °C and duration of 10 to 24 h to obtain a compound of formula (Ib)



(Ib)

where 'Hal' represents a halogen atom selected bromine or iodine, R^2 is hydrogen and R^3 and R^4 are as defined.

ii. Conversion of the compound of formula (Ib), to a compound of formula (Ic)

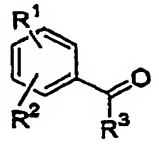


(Ic)

where R^1 represent aryl group, R^2 represents hydrogen atom and R^3 and R^4 are as defined, in a Suzuki coupling reaction manner, by using aryl boronic acid with palladium catalyst like $Pd(PPh_3)_4$, $PdCl_2$, $Pd(dba)_2$. The solvent used is selected from terahydrofuran,

dioxane, acetonitrile, dimethylether, diethylether, dimethylformamide or a mixture thereof at reflux temperature of the solvent used for a period of 15 to 28 h.

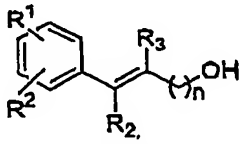
Alternatively, the compound of formula (Ic), is prepared from compound of formula (Ia')



(Ia')

where R^1, R^2 and R^3 are as defined, by using substituted phosphone acetate compounds selected from triethyl phosphono acetates, trimethylphosphono acetate or Ph_3P^+-CH_2^--CO_2Et.

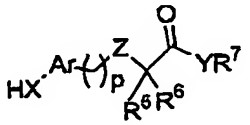
iii. The reduction of the compound of formula (Ic) to a compound of formula (Id)



(Id)

where R^1 represent aryl group, R^2 represents hydrogen atom and R^3 and R^4 are as defined, is carried out in the presence of a reducing agent selected from DIBAL-H, AlH_3 or lithium aluminium (LAH). The solvent used in the reaction is selected from toluene, tetrahydrofuran, ether, dioxane, dimethoxyethane or a mixture thereof at a temperature range of -90 to -25 °C, for a duration of 0.5 h to 2 h. The temperature and duration of the reaction can be decreased in the presence of AlH_3.

iv. Coupling of a compound of formula (Id) with a compound of formula (Ie)



(Ie)

where p represents 1, Y represents O or S, R^5 and R^6 are as defined, R^7 is as defined except hydrogen to obtain compound of formula (I), where p represents 1, Y represents O or S, R^7 represents all the groups as defined , except hydrogen atom and all other symbols are as defined, by using PPh_3, DIAD or DEAD. The solvent used in the reaction is selected from tetrahydrofuran, toluene, benzene or a mixture thereof at a temperature range of 20 to 40 °C, for duration of 40 to 80 h.

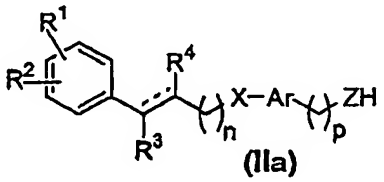
v. Hydrolysis of the compound of general formula (I) where R^7 represents hydrogen atom, Y represents O or S, p represents 1 and all other symbols are as defined

earlier, is obtained from a compound of formula (I) where R^7 represents all groups defined earlier except hydrogen, Y represents O or S, p represents 1 and all other symbols are as defined earlier, in the presence of a base selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate or sodium carbonate. The solvent used is selected from alcohols selected from methanol, ethanol, propanol, isopropanol or a mixture thereof, water, tetrahydrofuran, dioxane, ether or a mixture thereof at a temperature range of 30 to 80 °C, for duration of 2 to 24 h.

vi. The compound of general formula (I) where Z represents O or S, p represents 1 and R^7 represents hydrogen or alkyl group are converted to compound of formula (I), where Y represents NR^{11} by reacting with an amine of the formula NHR^7R^{11}, where R^7 and R^{11} are as defined to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier. Alternatively, the compound of formula (I) where YR^7 represents OH are converted to acid halide, preferably where YR^7 = Cl, by reacting with reagents selected from oxalyl chloride or thionyl chloride, followed by treatment with an amine of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier. Alternatively, mixed anhydrides are obtained from compound of formula (I) where YR^7 represents OH and all other symbols are as defined earlier by treating with acid halide selected from acetyl chloride, acetyl bromide, pivaloyl chloride or dichlorobenzoyl chloride. The reaction can be carried out in the presence of pyridine, triethylamine or diisopropyl ethylamine. Coupling reagent selected from DCC/DMAP DCC/HOBt, EDCI/HOBT, DIC/HOBt, ethylchloroformate, isobutylchloroformate can be used to activate the acid. The solvent used is selected from halogenated hydrocarbon like $CHCl_3$ or CH_2Cl_2; hydrocarbon like benzene, toluene, xylene or a mixture thereof at a temperature range of –40 to 40 °C. The acid halide or mixed anhydride or activated acid obtained by coupling reagents described above thus prepared may further be treated with an amine of the formula NHR^7R^{11} where R^7 and R^{11} are as defined earlier, to yield a compound of formula (I) where Y represents NR^{11} and all other symbols are as defined earlier.

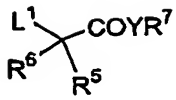
or

b) The reaction of compound of formula (IIa)



(IIa)

where all symbols are as defined in claim 1, with a compound of formula (IIb)

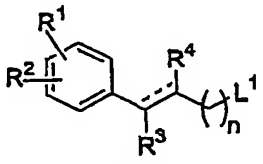


(IIb)

where L^1 is a leaving group selected from hydroxy, halogen atom, *p*-toluenesulfonate, methanesulfonate or trifluoromethanesulfonate, and all other symbols are as defined, is carried out in the presence of a solvent selected from THF, DMF, DMSO, DME, toluene, benzene, xylene or a mixture thereof in the presence of a base selected from K_2CO_3, Na_2CO_3, $NaNH_2$, n-BuLi, NaH, KH, trichylamine, collidinc, lutidine or a mixture thereof optionally in an inert atmosphere of nitrogen, helium or argon at a temperature range of 0 to 120 °C, for a duration of 1 to 72 h.

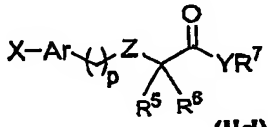
or

c) The reaction of compound of formula (IIc)



(IIc)

where L^1 represents a leaving group selected from hydroxy, halogen atom, *p*-toluenesulfonate, methanesulfonate or trifluoromethanesulfonate, and all other symbols are as defined, with compound of formula (IId)

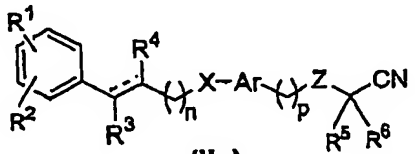


(IId)

where all symbols are as defined, is carried out in the presence of a solvent selected from THF, DMF, DMSO, DME or a mixture thereof optionally in an inert atmosphere of nitrogen, argon or helium in the presence of a base selected from K_2CO_3, Na_2CO_3 or NaH, KH, triethyl amine or a mixture thereof at a temperature range of 0 to 120 °C and duration of 1 to 72 h.

or

d) The conversion of compound of formula (IIe)



(IIe)

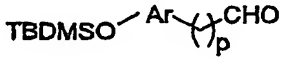
where all symbols are as defined, to a compound of formula (I), where YR^7 represents OH and all other symbols are as defined, is carried out either in the presence of a base or an acid. Selection of base or an acid is not critical. Any base normally used for the hydrolysis of nitrile to an acid can be employed, metal hydroxide selected from NaOH or KOH in an aqueous solvent or any acid normally used for hydrolysis of nitrile to ester can be employed selected from dry HCl in an excess of alcohol like methanol, ethanol, propanol, isopropanol or a mixture thereof at a temperature range 0 °C to 150 °C and duration of 0.25 to 48 h.

or

e) i. The compound of formula (IIIa)

(IIIa)

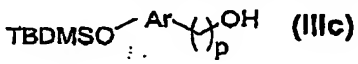
where Ar is as defined is converted to a compound of formula (IIIb)



(IIIb)

by reacting with TBDMS-Hal, $(CH_3)_3Si$-Hal or Ph_3C-Hal where 'Hal' represents halogen atom in the presence of a base used selected from triethylamine, Na_2CO_3 or K_2CO_3 and a solvent selected from dichloromethane, tetrahydrofuran, chloroform, dimethylether, diethylether, dioxane, benzene, toluene or a mixture thereof at a temperature range of 0 °C to room temperature and duration of 8 to 20 h.

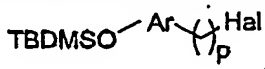
ii. The compound of formula (IIIb) is converted to a compound of formula (IIIc)



(IIIc)

by using $NaBH_4$ in the presence of an alcohol selected from methanol, ethanol, propanol, isopropanol or a mixture thereof as a solvent at room temperature for a duration of 1 to 4 h.

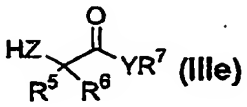
iii. The compound of formula (IIIc) is converted to a compound of formula (IIId)



(IIId)

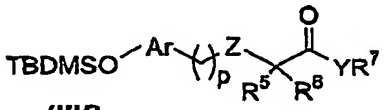
in the presence of $C(Hal)_4$, where 'Hal' represents halogen atom in the presence of PPh_3 and a solvent selected from dichloromethane, tetrahydrofuran, chloroform, dimethylether, diethylether, dioxane, benzene, toluene or a mixture thereof at room temperature for a duration of 0.5 to 2 h.

iv. The compound of formula (IIId) is reacted with the compound of formula (IIIe)



(IIIe)

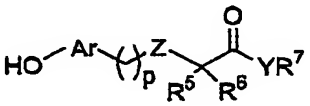
where all the symbols are as defined, to obtain a compound of formula (IIIf)



(IIIf)

where all the symbols are as defined. The reaction is carried out in the presence of a base selected from NaH, KH, sodium amide or potassium tertiary butoxide in the presence of a selected from DMSO, THF, toluene, benzene or a mixture thereof at a temperature range of 50 to 90 °C, for a period of 8 to 15 h.

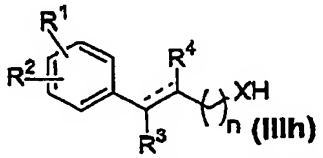
v. The deprotection of compound of formula (IIIf) to obtain a compound of formula (IIIg)



(IIIg)

where all the symbols are as defined, is carried out by using tetrabutylammoniumfluoride (TBAF) in the presence of a solvent selected from water, THF, dioxane, dichloromethane, chloroform, methanol, ethanol or a mixture thereof at a temperature range of 20 to 40 °C and duration of 1 to 6 h.

vi. The compound of formula (IIIg) is reacted with the compound of formula (IIIh)



(IIIh)

where all the symbols are as defined, to obtain a compound of formula (I), where Y represents O or S, R^7 represents all groups as defined except hydrogen. The reaction is carried out by using PPh_3, diisopropyl azadicarboxylate (DIAD), or diethyl azadicarboxylate (DEAD) in the presence of a solvent selected from tetrahydrofuran, toluene, benzene or a mixture thereof at a temperature range of 20 to 40 °C and duration of 40 to 80 h.

vii) The compound of general formula (I) where R^7 represents hydrogen atom, Y represents O or S, p represents 1 and all other symbols are as defined, is obtained from

compound of formula (I) where R^7 represents all groups are as defined except hydrogen, Y represents O or S, p represents 1 and all other symbols are as defined, by hydrolysis using conventional methods. The reaction is carried out in the presence of a base selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, potassium carbonate or sodium carbonate in the presence of a solvent alcohol like methanol, ethanol, propanol, isopropanol or a mixture thereof, water, tetrahydrofuran, dioxane, ether or a mixture thereof at a temperature range of 30 to 80 °C and duration of 2 to 24 h.

16. The substituents on the fused rings formed by R^1 and R^2 are selected from (C_1-C_{10})alkyl, halogen, hydroxy, halo(C_1-C_{10})alkyl, nitro, amino, cyano, oxo, or thioxo.

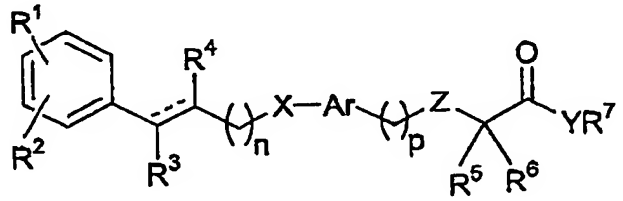
The substituents on R^1 and R^2 are selected from halogen, hydroxy, nitro, amino, oxo, thioxo, optionally substituted groups selected from (C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})alkoxy, aryl, aralkyl, (C_1-C_{10})alkylsulfonyl, (C_1-C_{10})alkylsulinyl, (C_1-C_{10})alkylsulfanyl, (C_1-C_{10})alkylsulfonyloxy, (C_1-C_{10})alkylsulinyloxy, (C_1-C_{10})alkylsulfanyloxy. The substituents are selected from halogen, hydroxyl, nitro, amino, cyano or (C_1-C_{10})alkyl.

Cyclic rings formed by R^5 and R^6 are selected from cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl.

The substituents on R, R^3, R^4, R^7 and R^{11} are selected from halogen, nitro, amino, hydroxy, (C_1-C_{10})alkyl, oxo, aralkyl

The substitutents on R^5 , R^6 and R^7 are selected from halogen, hydroxy, nitro, (C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_{10})alkoxy, aryl, aralkyl, aralkoxy(C_1-C_{10})alkyl, heterocyclyl, heteroaryl, amino.

17. A pharmaceutical composition, which comprises a compound of formula (I)



(I)

as defined in claims 1to 7 and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

18. A pharmaceutical composition as claimed in claim 17 in the form of a tablet, capsule, powder, syrup, solution or suspension.

19. A method for treating and/or preventing dyslipidemia comprising administering a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 to a patient in need thereof.

20. A method for treating and/or preventing diabetes caused by insulin resistance or impaired glucose tolerance comprising administering a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 to a patient in need thereof.

21. Use of a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 for treating and/or preventing dyslipidemia.

22. Use of a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 for treating and/or preventing diabetes caused by insulin resistance or impaired glucose tolerance.

23. A medicine for treating and/or preventing diabetes caused dyslipidemia comprising administering a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 to a patient in need thereof

24. A medicine for treating and/or preventing diabetes caused by insulin resistance or impaired glucose tolerance comprising administering a compound of formula (I) as defined in claims 1 to 14 or a pharmaceutical composition according to claim 17 to a patient in need thereof